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(54) Title: COMPOSITIONS AND METHODS RELATING TO ANTI IGF-1 RECEPTOR ANTIBODIES

(57) Abstract: The present invention provides compositions and methods relating to or derived from anti-IGF-1R antibodies. In particular embodiments, the invention provides fully human, humanized, or chimeric antiIGF-1R antibodies that bind human IGF-1R, IGF-1R-binding fragments and derivatives of such antibodies, and IGF-1R-binding polypeptides comprising such fragments. Other embodiments provide nucleic acids encoding such antibodies, antibody fragments and derivatives and polypeptides, cells comprising such polynucleotides, methods of making such antibodies, antibody fragments and derivatives and polypeptides, and methods of using such antibodies, antibody fragments and derivatives and polypeptides, including methods of treating or diagnosing subjects having IGF-1R-related disorders or conditions.

COMPOSITIONS AND METHODS RELATING TO ANTI-IGF-1 RECEPTOR ANTIBODIES

5   **REFERENCE TO RELATED APPLICATION**

This application claims the benefit of U.S. Provisional Application Ser. No. 60/638,961, filed on December 22, 2004, and is incorporated by reference herein.

10   **FIELD OF THE INVENTION**

This application provides compositions and methods relating to anti-IGF-1 receptor antibodies.

BACKGROUND OF THE INVENTION

Insulin-like growth factors 1 and 2 (IGF-1 and IGF-2, respectively) promote the differentiation and

15   proliferation of a wide variety of mammalian cell types.

IGF-1 and IGF-2 both circulate widely throughout the body in plasma. They exert their effects on cells by binding to and activating the IGF-1 receptor (IGF-1R). IGF-1R is a member of the family of tyrosine kinase growth factor receptors. Its amino acid sequence is about 70% identical to that of the insulin receptor.

20   Abnormal IGF-1, IGF-2, and/or IGF-1R activities are associated with a number of medical conditions, including various types of cancer, growth defects (*e.g.*, acromegaly, gigantism, and small stature), psoriasis, atherosclerosis, post angioplasty smooth muscle restonsis of blood vessels, diabetes, microvasular proliferation, neuropathy, loss of muscle mass, and osteoporosis.

25   **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 provides nucleotide sequences encoding light chain variable domains L1 through L52 and heavy chain variable domains H1 through H52.

Figure 2 provides amino acid sequences of light chain variable domains L1 through L52. CDR and FR regions are indicated.

30   Figure 3 provides amino acid sequences of heavy chain variable domains H1 through H52. CDR and FR regions are indicated.

Figure 4 provides amino acid sequences of the light chain CDR1 regions of light chain variable domains L1 through L52. Consensus sequences for groups of related CDR sequences are also provided.

Figure 5 provides amino acid sequences of the light chain CDR2 regions of light chain variable

35   domains L1 through L52. Consensus sequences for groups of related CDR sequences are also provided.

Figure 6 provides amino acid sequences of the light chain CDR3 regions of light chain variable domains L1 through L52. Consensus sequences for groups of related CDR sequences are also provided.

Figure 7 provides amino acid sequences of the heavy chain CDR1 regions of heavy chain variable domains H1 through H52. Consensus sequences for groups of related CDR sequences are also provided.

40   Figure 8 provides amino acid sequences of the heavy chain CDR2 regions of heavy chain variable domains H1 through H52. Consensus sequences for groups of related CDR sequences are also provided.

Figure 9 provides amino acid sequences of the heavy chain CDR3 regions of heavy chain variable domains H1 through H52. Consensus sequences for groups of related CDR sequences are also provided.

Figure 10 provides the amino acid sequence of a human IGF-1R extracellular domain fused to a human IgG1 Fc region (underlined) with an intervening caspace-3 cleavage site (bold).

5   Figure 11 provides the amino acid sequence of a human insulin receptor extracellular domain fused to a human IgG1 Fc region (underlined).

Figure 12 provides the protein sequence of a human IGF-1R extracellular domain (including signal peptide) fused at the C-terminus with chicken avidin. The initiating met in the IGF-1R ECD is designated position 1 in this figure.

10   Figure 13 provides the polypeptide sequence of a human kappa light chain antibody constant region and a human IgG1 heavy chain antibody constant region.

Figure 14 provides a graph illustrating that four phage-displayed antibodies bind significantly better to an IGF-1R-Fc molecule than they bind to an insulin-receptor-Fc or a murine Fc.

Figure 15 provides graphs illustrating the ability of certain antibodies to compete for binding to

15   IGF-1R with IGF-1 and IGF-2.

Figure 16 provides graphs illustrating the ability of certain antibodies to inhibit the growth of 32D hu IGF-1R+IRS-1 cells.

Figure 17 provides graphs illustrating the ability of certain antibodies to inhibit the growth of Balb/C 3T3 hu IGF-1R cells.

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SUMMARY OF THE INVENTION

In one aspect, the present invention provides an isolated antigen binding protein comprising either: a. a light chain CDR3 comprising a sequence selected from the group consisting of: i. a light chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions

25   from a CDR3 sequence selected from the group consisting of the light chain CDR3 sequences of L1-L52 as shown in Figure 6; ii. $M X_1 X_2 X_3 X_4 X_5 P X_6 X_7$; iii. $Q Q X_8 X_9 X_{10} X_{11} P X_{12} T$; and iv. $Q S Y X_{13} X_{14} X_{15} N X_{16} X_{17} X_{18}$; b. a heavy chain CDR3 comprising a sequence selected from the group consisting of: i. a heavy chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence selected from the group consisting of the heavy chain

30   CDR3 sequences of H1-H52 as shown in Figure 9; ii. $X_{19} X_{20} X_{21} X_{22} X_{23} X_{24} X_{25} X_{26} X_{27} F D I$; iii. $X_{28} X_{29} X_{30} X_{31} X_{32} X_{33} X_{34} X_{35} X_{36} X_{37} X_{38} M D V$; iv. $D S S X_{39}$; or c. the light chain CDR3 sequence of (a) and the heavy chain CDR3 sequence of (b); wherein X_1 is a glutamine residue or a glutamate residue, X_2 is an alanine residue, a glycine residue, a threonine residue, or a serine residue, X_3 is a leucine residue, a phenylalanine residue, or a threonine residue, X_4 is glutamine residue, a glutamate residue, or a histidine

35   residue, X_5 is a threonine residue, a methionine residue, a tryptophan residue, or a valine residue, X_6 is a glycine residue, an alanine residue, a valine residue, a leucine residue, an isoleucine residue, a proline residue, a phenylalanine residue, a methionine residue, a tryptophan residue, or a cysteine residue, X_7 is threonine residue, an alanine residue, or a serine residue, X_8 is an arginine residue, a serine residue, a leucine residue, or an alanine residue, X_9 is an asparagine residue, a serine residue, or a histidine residue,

40   X_{10} is an asparagine residue or a serine residue, X_{11} is a tryptophan residue, a valine residue, a tyrosine

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residue, a proline residue, or a phenylalanine residue, X_{12} is a leucine residue, a tyrosine residue, or an isoleucine residue, X_{13} is an aspartate residue or a glutamine residue, X_{14} is a serine residue or a proline residue, X_{15} is a serine residue, a tyrosine residue, an aspartate residue, or an alanine residue, X_{16} is a glutamine residue, an arginine residue, a valine residue, or a tryptophan residue, X_{17} is an arginine residue,

5   a valine residue, an isoleucine residue, or no residue, X_{18} is a valine residue or no residue, X_{19} is a glutamate residue or no residue, X_{20} is a tyrosine residue, a glycine residue, a serine residue, or no residue, X_{21} is a serine residue, an asparagine residue, a tryptophan residue, a glutamate residue, as aspartate residue, or no residue, X_{22} is a serine residue, an aspartate residue, a tryptophan residue, an alanine residue, an arginine residue, a threonine residue, a glutamine residue, a leucine residue, a glutamate residue, or no residue, X_{23} is

10   a serine residue, a glycine residue, an asparagine residue, a threonine residue, a tryptophan residue, a valine residue, an alanine residue, or an isoleucine residue, X_{24} is an arginine residue, a glutamine residue, a tyrosine residue, a valine residue, an alanine residue, a glycine residue, a serine residue, a phenylalanine residue, or a tryptophan residue, X_{25} is an asparagine residue, a leucine residue, an aspartate residue, a threonine residue, a tryptophan residue, a tyrosine residue, a valine residue, an alanine residue, or a

15   histidine residue, X_{26} is an aspartate residue, a serine residue, an asparagine residue, or a glutamine residue, X_{27} is an alanine residue or a proline residue, X_{28} is an alanine residue or no residue, X_{29} is a glutamate residue, a tyrosine residue, a glycine residue, or no residue, X_{30} is an arginine residue, a serine residue, or no residue, X_{31} is a glycine residue, an aspartate residue, a valine residue, a serine residue, or no residue, X_{32} is a serine residue, an aspartate residue, a glycine residue, or no residue, X_{33} is a phenylalanine residue, an

20   aspartate residue, a tyrosine residue, a glycine residue, a serine residue, a histidine residue, a tryptophan residue, or no residue, X_{34} is a tryptophan residue, an aspartate residue, a tyrosine residue, a serine residue, or no residue, X_{35} is an aspartate residue, a glutamate residue, an arginine residue, a serine residue, a glycine residue, a tyrosine residue, or a tryptophan residue, X_{36} is a tyrosine residue, a lysine residue, an isoleucine residue, a leucine residue or a phenylalanine residue, X_{37} is a tyrosine residue, a serine residue, a

25   phenylalanine residue, an aspartate residue, or a glycine residue, X_{38} is a glycine residue, an asparagine residue, or a tyrosine residue, X_{39} is a valine residue, a glycine residue, or a serine residue, and said antigen binding protein binds specifically to human IGF-1R. In one embodiment, the isolated antigen binding protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions

30   from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions,

35   substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding

40   protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1

sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of two amino acid

5   additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more

10   than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain

15   CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions,

20   and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR3 sequence of L1-L52 as shown in Figure 6; c. a heavy chain CDR2 sequence that differs by no more

25   than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and d. a heavy chain CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of two amino

30   acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a heavy chain CDR2 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR2 sequence of H1-H52 as shown in Figure 8; and c. a heavy chain CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises an amino acid sequence selected from the group consisting of: a. a light chain CDR1 sequence that differs by

35   no more than a total of one amino acid addition, substitution, or deletion from a CDR1 sequence of L1-L52 as shown in Figure 4; and b. a heavy chain CDR2 sequence of H1-H52 as shown in Figure 8. In another embodiment, the isolated antigen binding protein comprises a CDR1 sequence of L1-L52 as shown in Figure 4. In another embodiment, the isolated antigen binding protein comprises a sequence selected from the group consisting of: a. a light chain CDR1 sequence selected from the group consisting of: i.

40   RSSQSLLHSNGYNYLD; ii. RASQ(G/S)(I/V)(G/S)X(Y/F)L(A/N); and iii. RSSQS(L/I)XXXXX; b. a

light chain CDR2 sequence selected from the group consisting of: i. LGSNRAS; ii. AASTLQS; and iii. EDNXRPS; c. a heavy chain CDR1 sequence selected from the group consisting of: i. SSNWWS; ii. XYYWS; and iii. SYAM(S/H); and d. a heavy chain CDR2 sequence selected from the group consisting of: i. (E/I)(I/V)(Y/N)(H/Y)SGST(N/Y)YNPSLKS; and ii. XIS(G/S)SG(G/S)STYYADSVKG; wherein amino acid residue symbols enclosed in parentheses identify alternative residues for the same position in a sequence, each X is independently any amino acid residue, and each Z is independently a glycine residue, an alanine residue, a valine residue, a leucine residue, an isoleucine residue, a proline residue, a phenylalanine residue, a methionine residue, a tryptophan residue, or a cysteine residue. In another embodiment, the isolated antigen binding protein comprises a heavy chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises a heavy chain CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises a heavy chain CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises two amino acid sequences selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises three amino acid sequences selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises four amino acid sequences selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of six

amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or

5   deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino

10 acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises five amino acid sequences selected from the group consisting of: a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions,

15 substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a

20 total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises: a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1

25 sequence of L1-L52 as shown in Figure 4; b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5; c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6; d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions,

30 and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7; e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9. In another embodiment, the isolated antigen binding protein comprises either: a.

35 a light chain variable domain comprising: i. a light chain CDR1 sequence shown in Figure 4; ii. a light chain CDR2 sequence shown in Figure 5; and iii. a light chain CDR3 sequence shown in Figure 6; b. a heavy chain variable domain comprising: i. a heavy chain CDR1 sequence shown in Figure 7; ii. a heavy chain CDR2 sequence shown in Figure 8; and iii. a heavy chain CDR3 sequence shown in Figure 9; or c. the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment,

40 the isolated antigen binding protein comprises either: a. light chain CDR1, CDR2, and CDR3 sequences

that each is identical to the CDR1, CDR2, and CDR3 sequences, respectively, of the same light chain variable domain sequence selected from the group consisting of L1-L52; b. heavy chain CDR1, CDR2, and CDR3 sequences that each is identical to the CDR1, CDR2, and CDR3 sequences, respectively, of the same heavy chain variable domain sequence selected from the group consisting of H1-H52; or c. the light chain

5   CDR1, CDR2, and CDR3 sequences of (a) and the heavy chain CDR1, CDR2, and CDR3 sequences of (b).

In another aspect, the present invention provides an isolated antigen binding protein comprising either: a. a light chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 80% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 15 contiguous amino acid residues of a light chain

10   variable domain sequence of L1-L52 as shown in Figure 2; iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of a light chain variable domain sequence of L1-L52 as shown in Figure 1; b. a

15   heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 80% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 15 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding a heavy chain

20   variable domain sequence of H1-H52 as shown in Figure 1; and iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c. the light chain variable domain of (a) and the heavy chain variable domain of (b); wherein said antigen binding protein binds to human IGF-1R. In one embodiment, the isolated antigen binding protein

25   comprises either: a. a light chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 85% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 25 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 85% identical to a polynucleotide sequence encoding a

30   light chain variable domain sequence of L1-L52 as shown in Figure 1; and iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under highly stringent conditions to the complement of a polynucleotide consisting of a light chain variable domain sequence of L1-L52 as shown in Figure 1; b. a heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 85% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; ii. a

35   sequence of amino acids comprising at least 25 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 85% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; and iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under highly stringent conditions to the complement of a

40   polynucleotide consisting of a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c)

the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen binding protein comprises either: a. a light chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 90% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 35

5   contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 90% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and b. a heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 90% identical to a heavy chain variable domain sequence of H1-H52 as shown in

10   Figure 2; ii. a sequence of amino acids comprising at least 35 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 90% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c) the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen .

15   binding protein comprises either: a. a light chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 95% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 50 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 95% identical to a polynucleotide

20   sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and b. a heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 95% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 50 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide

25   sequence that is at least 95% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c) the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen binding protein comprises either: a. a light chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 97% identical to a light chain variable domain sequence of L1-L52 as shown in Figure

30   2; ii. a sequence of amino acids comprising at least 75 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 97% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and b. a heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 97% identical to a heavy chain

35   variable domain sequence of H1-H52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 75 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 97% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c) the light chain variable domain of (a) and the heavy chain variable domain of (b).

40   In another embodiment, the isolated antigen binding protein comprises either: a. a light chain variable

domain sequence selected from the group consisting of: i. a sequence of amino acids at least 99% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 90 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and iii. a sequence of amino acids encoded by a polynucleotide sequence that is at

5 least 99% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and b. a heavy chain variable domain sequence selected from the group consisting of: i. a sequence of amino acids at least 99% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; ii. a sequence of amino acids comprising at least 90 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and iii. a

10 sequence of amino acids encoded by a polynucleotide sequence that is at least 99% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or c. the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen binding protein comprises either: a. a light chain variable domain sequence selected from the group consisting of L1-L52 as shown in Figure 2; b. a heavy chain variable

15 domain sequence selected from the group consisting of H1-H52 as shown in Figure 3; or c. the light chain variable domain of (a) and the heavy chain variable domain of (b). In another embodiment, the isolated antigen binding protein comprises a combination of a light chain variable domain and a heavy chain variable domain selected from the group of combinations consisting of: L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17,

20 L18H18, L19H19, L20, H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52. In another embodiment, the isolated antigen binding protein further comprises: a. the kappa light chain constant sequence of Figure 13, b. the IgG1 heavy chain constant sequence of Figure

25 13, or c. the kappa light chain constant sequence of Figure 13 and the IgG1 heavy chain constant sequence of Figure 13. In another embodiment, the isolated antigen binding protein, when bound to IGF-1R: a. inhibits IGF-1R; b. activates IGF-1R; c. cross-competes with a reference antibody for binding to IGF-1R; d. binds to the same epitope of IGF-1R as said reference antibody; e. binds to IGF-1R with substantially the same Kd as said reference antibody; or f. binds to IGF-1R with substantially the same off rate as said

30 reference antibody; wherein said reference antibody comprises a combination of light chain and heavy chain variable domain sequences selected from the group of combinations consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20, H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37,

35 L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52. In another embodiment, the isolated antigen binding protein, when bound to a human IGF-1R, inhibits binding of IGF-1 and/or IGF-2 to said human IGF-1R. In another embodiment, the isolated antigen binding protein inhibits the growth of a cancer cell by greater than about 80% in the presence of a growth stimulant selected from the group consisting of serum, IGF-1, and IGF-2.

40 In another embodiment, said cancer cell is an MCF-7 human breast cancer cell. In another embodiment, the

isolated antigen binding protein binds to human IGF-1R with a selectivity that is at least fifty times greater than its selectivity for human insulin receptor. In another embodiment, the isolated antigen binding protein inhibits tumor growth *in vivo*. In another embodiment, the isolated antigen binding protein inhibits IGF-1R mediated tyrosine phosphorylation. In another embodiment, the isolated antigen binding protein

5   specifically binds to the IGF-1R of a non-human primate, a cynomologous monkey, a chimpanzee, a non-primate mammal, a rodent, a mouse, a rat, a hamster, a guinea pig, a cat, or a dog. In another embodiment, the isolated antigen binding protein comprises: a. a human antibody; b. a humanized antibody; c. a chimeric antibody; d. a monoclonal antibody; e. a polyclonal antibody; f. a recombinant antibody; g. an antigen-binding antibody fragment; h. a single chain antibody; i. a diabody; j. a triabody; k. a tetrabody; l.

10   a Fab fragment; m. a F(ab')$_2$ fragment; n. a domain antibody; o. an IgD antibody; p. an IgE antibody; q. an IgM antibody; r. an IgG1 antibody; s. an IgG2 antibody; t. an IgG3 antibody; u. an IgG4 antibody; or v. an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond.

In another aspect, the present invention provides an isolated polynucleotide comprising a sequence

15   that encodes the light chain, the heavy chain, or both of said antigen binding protein. In one embodiment, said polynucleotide comprises a light chain variable domain nucleic acid sequence of Figure 1 and/or a heavy chain variable domain nucleic acid sequence of Figure 1. In another embodiment, a plasmid comprises said isolated polynucleotide. In another embodiment, said plasmid is an expression vector. In another embodiment, an isolated cell comprises said polynucleotide. In another embodiment, a

20   chromosome of said cell comprises said polynucleotide. In another embodiment, said cell is a hybridoma. In another embodiment, an expression vector comprises said polynucleotide. In another embodiment, said cell is a CHO cell. In another embodiment, the present invention provides a method of making an antigen binding protein that binds human IGF-1R, comprising incubating said isolated cell under conditions that allow it to express said antigen binding protein.

25   In another aspect, the present invention provides a pharmaceutical composition comprising the antigen binding protein. In one embodiment, the present invention provides a method of treating a condition in a subject comprising administering to said subject said pharmaceutical composition, wherein said condition is treatable by reducing the activity of IGF-1R in said subject. In another embodiment, said subject is a human being. In another embodiment, said condition is multiple myeloma, a liquid tumor, liver

30   cancer, a thymus disorder, a T-cell mediated autoimmune disease, an endocronological disorder, ischemia, or a neurodegenerative disorder. In another embodidment, said liquid tumor is selected from the group consisting of acute lymphocytic leukemia (ALL) and chronic myelogenous leukemia (CML); wherein said liver cancer is selected from the group consisting of hepatoma, hepatocellular carcinoma, cholangiocarcinoma, angiosarcomas, hemangiosarcomas, hepatoblastoma; wherein said thymus disorder is

35   selected from the group consisting of thymoma and thyroiditis, wherein said T-cell mediated autoimmune disease is selected from the group consisting of Multiple Sclerosis, Rheumatoid Arthritis, Systemic Lupus Erythematosus (SLE), Grave's Disease, Hashimoto's Thyroiditis, Myasthenia Gravis, Auto-Immune Thyroiditis, Bechet's Disease, wherein said endocrinological disorder is selected from the group consisting of Type II Diabetes, hyperthyroidism, hypothyroidism, thyroiditis, hyperadrenocorticism, and

40   hypoadrenocorticism; wherein said ischemia is post cardiac infarct ischemia, or wherein said

neurodegenerative disorder is Alzheimer's Disease. In another embodiment, said condition is selected from the group consisting of acromegaly, bladder cancer, Wilm's tumor, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervical cancer, synovial sarcoma, diarrhea associated with metastatic carcinoid, vasoactive intestinal

5   peptide secreting tumors, gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels, inappropriate microvascular proliferation, glioblastoma, medulloblastoma, head and neck squamous cell cancer, oral cancer, oral leukoplakia, prostate intraepithelial neoplasia, anal cancer, esophageal cancer, gastric cancer, bone cancer, metastatic cancer, polycythemia rubra vera, a benign condition related to oxidative stress, retinopathy of prematurity, Acute Respiratory Distress Syndrome, an overdose of

10   acetaminophen, bronchopulmonary dysplasia, cystic fibrosis, lung fibrosis, and diabetic retinopathy. In another embodiment, the method further comprising administering to said subject a second treatment. In another embodiment, said second treatment is administered to said subject before and/or simultaneously with and/or after said pharmaceutical composition is administered to said subject. In another embodiment, said second treatment comprises radiation treatment, surgery, or a second pharmaceutical composition. In

15   another embodiment, said second pharmaceutical composition comprises an agent selected from the group consisting of a corticosteroid, an anti-emetic, ondansetron hydrochloride, granisetron hydrochloride, metroclopramide, domperidone, haloperidol, cyclizine, lorazepam, prochlorperazine, dexamethasone, levomepromazine, tropisetron, a cancer vaccine, a GM-CSF inhibiting agent, a GM-CSF DNA vaccine, a cell-based vaccine, a dendritic cell vaccine, a recombinant viral vaccine, a heat shock protein (HSP)

20   vaccine, an allogeneic tumor vaccine, an autologous tumor vaccine, an analgesic, ibuprofen, naproxen, choline magnesium trisalicylate, an oxycodone hydrochloride, an anti-angiogenic agent, an anti-vascular agent, bevacizumab, an anti-VEGF antibody, an anti-VEGF receptor antibody, a soluble VEGF receptor fragment, an anti-TWEAK antibody, an anti-TWEAK receptor antibody, a soluble TWEAK receptor fragment, AMG 706, AMG 386, an anti-proliferative agent, a farnesyl protein transferase inhibitor, an $\alpha v \beta 3$

25   inhibitor, an $\alpha v \beta 5$ inhibitor, a p53 inhibitor, a Kit receptor inhibitor, a ret receptor inhibitor, a PDGFR inhibitor, a growth hormone secretion inhibitor, an angiopoietin inhibitor, a tumor infiltrating macrophage-inhibiting agent, a c-fms inhibiting agent, an anti-c-fms antibody, an CSF-1 inhibiting agent, an anti-CSF-1 antibody, a soluble c-fms fragment, pegvisomant, gemcitabine, panitumumab, irinothecan, and SN-38. In another embodiment, said method comprises administering to said subject a third treatment. In another

30   embodiment, said condition is a cancer, said second treatment comprises administering panitumumab, and said third treatment comprises administering gemcitabine. In another embodiment, said condition is selected from the group consisting of acromegaly, bladder cancer, Wilm's tumor, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervical cancer, synovial sarcoma, diarrhea associated with metastatic carcinoid, vasoactive

35   intestinal peptide secreting tumors, gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels, inappropriate microvascular proliferation, glioblastoma, medulloblastoma, head and neck squamous cell cancer, oral cancer, oral leukoplakia, prostate intraepithelial neoplasia, anal cancer, esophageal cancer, gastric cancer, bone cancer, metastatic cancer, polycythemia rubra vera, a benign condition related to oxidative stress, retinopathy of prematurity, Acute Respiratory Distress Syndrome, an

overdose of acetaminophen, bronchopulmonary dysplasia, cystic fibrosis, lung fibrosis, and diabetic retinopathy.

In another aspect, the present invention provides a method of increasing the longevity of a subject comprising administering to said subject said pharmaceutical composition.

5   In another aspect, the present invention provides a method of decreasing IGF-1R activity in a subject in need thereof comprising administering to said subject said pharmaceutical composition.

In another aspect, the present invention provides a method of decreasing IGF-1R signaling in a subject in need thereof comprising administering to said subject said pharmaceutical composition.

In another aspect, the present invention provides a method of inhibiting the binding of IGF-1
10   and/or IGF-2 to IGF-1R in a subject in need thereof comprising administering to said subject said pharmaceutical composition.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions, kits, and methods relating to molecules that bind to
15   the Insulin-Like Growth Factor Receptor ("IGF-1R"), including molecules that agonize or antagonize IGF-1R, such as anti-IGF-1R antibodies, antibody fragments, and antibody derivatives, *e.g.*, antagonistic anti-IGF-1R antibodies, antibody fragments, or antibody derivatives. Also provided are nucleic acids, and derivatives and fragments thereof, comprising a sequence of nucleotides that encodes all or a portion of a polypeptide that binds to IGF-1R, *e.g.*, a nucleic acid encoding all or part of an anti-IGF-1R antibody,
20   antibody fragment, or antibody derivative, plasmids and vectors comprising such nucleic acids, and cells or cell lines comprising such nucleic acids and/or vectors and plasmids. The provided methods include, for example, methods of making, identifying, or isolating molecules that bind to IGF-1R, such as anti-IGF-1R antibodies, methods of determining whether a molecule binds to IGF-1R, methods of determining whether a molecule agonizes or antagonizes IGF-1R, methods of making compositions, such as pharmaceutical
25   compositions, comprising a molecule that binds to IGF-1R, and methods for administering a molecule that binds IGF-1R to a subject, for example, methods for treating a condition mediated by IGF-1R, and for agonizing or antagonizing a biological activity of IGF-1R, IGF-1, and/or IGF-2 *in vivo* or *in vitro*.

Polynucleotide and polypeptide sequences are indicated using standard one- or three-letter abbreviations. Unless otherwise indicated, polypeptide sequences have their amino termini at the left and
30   their carboxy termini at the right and single-stranded nucleic acid sequences, and the top strand of double-stranded nucleic acid sequences, have their 5' termini at the left and their 3' termini at the right. A particular polypeptide or polynucleotide sequence also can be described by explaining how it differs from a reference sequence.

Polynucleotide and polypeptide sequences of particular light and heavy chain variable domains are
35   shown in Figures 1, 2 and 3,, where they are labeled, for example, L1 ("light chain variable domain 1"), H1 ("heavy chain variable domain 1"), *etc*. Antibodies comprising a light chain and heavy chain from Figures 2 and 3 are indicated by combining the name of the light chain and the name of the heavy chain variable domains. For example, "L4H7," indicates an antibody comprising the light chain variable domain of L4 and the heavy chain variable domain of H7.

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue

5 culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, *e.g.*, Sambrook *et al.* Molecular

10 Cloning: A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989) and Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates (1992), and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990), which are incorporated herein by reference. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art

15 or as described herein. The terminology used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

20 The following terms, unless otherwise indicated, shall be understood to have the following meanings:

The term "isolated molecule" (where the molecule is, for example, a polypeptide, a polynucleotide, or an antibody) is a molecule that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is substantially free of other

25 molecules from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a molecule that is chemically synthesized, or synthesized in a cellular system different from the cell from which it naturally originates, will be "isolated" from its naturally associated components. A molecule also may be rendered substantially free of naturally associated components by isolation, using purification techniques well known in the art. Molecule purity or homogeneity may be assayed by a

30 number of means well known in the art. For example, the purity of a polypeptide sample may be assayed using polyacrylamide gel electrophoresis and staining of the gel to visualize the polypeptide using techniques well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

The terms "IGF-1R inhibitor" and "IGF-1R antagonist" are used interchangeably. Each is a

35 molecule that detectably inhibits at least one function of IGF-1R. Conversely, an "IGF-1R agonist" is a molecule that detectably increases at least one function of IGF-1R. The inhibition caused by an IGF-1R inhibitor need not be complete so long as it is detectable using an assay. Any assay of a function of IGF-1R can be used, examples of which are provided herein. Examples of functions of IGF-1R that can be inhibited by an IGF-1R inhibitor, or increased by an IGF-1R agonist, include binding to IGF-1, IGF-12, and/or

40 another IGF-1R-activating molecule, kinase activity, downstream signaling, and so on. Examples of types

of IGF-1R inhibitors and IGF-1R agonists include, but are not limited to, IGF-1R binding polypeptides such as antigen binding proteins (e.g., IGF-1R inhibiting antiben binding proteins), antibodies, antibody fragments, and antibody derivatives.

The terms "peptide," "polypeptide" and "protein" each refers to a molecule comprising two or
5   more amino acid residues joined to each other by peptide bonds. These terms encompass, *e.g.*, native and artificial proteins, protein fragments and polypeptide analogs (such as muteins, variants, and fusion proteins) of a protein sequence as well as post-translationally, or otherwise covalently or non-covalently, modified proteins. A peptide, polypeptide, or protein may be monomeric or polymeric.

The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino-terminal
10   and/or carboxy-terminal deletion as compared to a corresponding full-length protein. Fragments can be, for example, at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 50, 70, 80, 90, 100, 150 or 200 amino acids in length. Fragments can also be, for example, at most 1,000, 750, 500, 250, 200, 175, 150, 125, 100, 90, 80, 70, 60, 50, 40, 30, 20, 15, 14, 13, 12, 11, or 10 amino acids in length. A fragment can further comprise, at either or both of its ends, one or more additional amino acids, for example, a sequence of amino acids from
15   a different naturally-occurring protein (*e.g.*, an Fc or leucine zipper domain) or an artificial amino acid sequence (*e.g.*, an artificial linker sequence).

Polypeptides of the invention include polypeptides that have been modified in any way and for any reason, for example, to: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (4) confer or modify
20   other physicochemical or functional properties. Analogs include muteins of a polypeptide. For example, single or multiple amino acid substitutions (*e.g.*, conservative amino acid substitutions) may be made in the naturally occurring sequence (*e.g.*, in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. A "conservative amino acid substitution" is one that does not substantially change the structural characteristics of the parent sequence (*e.g.*, a replacement amino acid should not tend to break
25   a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterize the parent sequence or are necessary for its functionality). Examples of art-recognized polypeptide secondary and tertiary structures are described in Proteins, Structures and Molecular Principles (Creighton, Ed., W. H. Freeman and Company, New York (1984)); Introduction to Protein Structure (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton *et at.* Nature 354:105 (1991), which are
30   each incorporated herein by reference.

The present invention also provides non-peptide analogs of IGF-1R binding polypeptides. Non-peptide analogs are commonly used in the pharmaceutical industry as drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics". Fauchere, J. Adv. Drug Res. 15:29 (1986); Veber and Freidinger TINS p.392 (1985);
35   and Evans *et al.* J. Med. Chem. 30:1229 (1987), which are incorporated herein by reference. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce an equivalent therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*i.e.*, a polypeptide that has a desired biochemical property or pharmacological activity), such as a human antibody, but have one or more peptide linkages optionally replaced by a linkage
40   selected from the group consisting of: --CH$_2$NH--, --CH$_2$S--, --CH$_2$--CH$_2$--, --CH=CH-(*cis* and *trans*), --

$COCH_2$--, --$CH(OH)CH_2$--, and --CH_2SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (*e.g.*, D-lysine in place of L-lysine) may also be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be

5   generated by methods known in the art (Rizo and Gierasch Ann. Rev. Biochem. 61:387 (1992), incorporated herein by reference), for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

A "variant" of a polypeptide (*e.g.*, an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence

10   relative to another polypeptide sequence. Variants of the invention include fusion proteins.

A "derivative" of a polypeptide is a polypeptide (*e.g.*, an antibody) that has been chemically modified, *e.g.*, via conjugation to another chemical moiety such as, for example, polyethylene glycol, albumin (*e.g.*, human serum albumin), phosphorylation, and glycosylation. Unless otherwise indicated, the term "antibody" includes, in addition to antibodies comprising two full-length heavy chains and two full-

15   length light chains, derivatives, variants, fragments, and muteins thereof, examples of which are described below.

An "antigen binding protein" is a protein comprising a portion that binds to an antigen and, optionally, a scaffold or framework portion that allows the antigen binding portion to adopt a conformation that promotes binding of the antigen binding protein to the antigen. Examples of antigen binding proteins

20   include antibodies, antibody fragments (e.g., an antigen binding portion of an antibody), antibody derivatives, and antibody analogs. The antigen binding protein can comprise, for example, an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the antigen binding protein as well as wholly synthetic scaffolds comprising,

25   for example, a biocompatible polymer. See, for example, Korndorfer et al., 2003, Proteins: Structure, Function, and Bioinformatics, Volume 53, Issue 1:121-129; Roque et al., 2004, Biotechnol. Prog. 20:639-654. In addition, peptide antibody mimetics ("PAMs") can be used, as well as scaffolds based on antibody mimetics utilizing fibronection components as a scaffold.

An antigen binding protein can have, for example, the structure of a naturally occurring

30   immunoglobulin. An "immunoglobulin" is a tetrameric molecule. In a naturally occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for

35   effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y.

(1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two binding sites.

Naturally occurring immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity

5 determining regions or CDRs. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat *et al.* in *Sequences of Proteins of Immunological Interest*, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991.

An "antibody" refers to an intact immunoglobulin or to an antigen binding portion thereof that

10 competes with the intact antibody for specific binding, unless otherwise specified. Antigen binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen binding portions include, *inter alia*, Fab, Fab', F(ab')$_2$, Fv, domain antibodies (dAbs), and complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies, triabodies, tetrabodies, and polypeptides that contain at least a portion of an

15 immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide.

A Fab fragment is a monovalent fragment having the V_L, V_H, C_L and C_H1 domains; a F(ab')$_2$ fragment is a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment has the V_H and C_H1 domains; an Fv fragment has the V_L and V_H domains of a single arm of an antibody; and a dAb fragment has a V_H domain, a V_L domain, or an antigen-binding fragment of a V_H or V_L

20 domain (US Pat. No. 6,846,634, 6,696,245, US App. Pub. No. 05/0202512, 04/0202995, 04/0038291, 04/0009507, 03/0039958, Ward *et al.*, Nature 341:544-546, 1989).

A single-chain antibody (scFv) is an antibody in which a V_L and a V_H region are joined via a linker (*e.g.*, a synthetic sequence of amino acid residues) to form a continuous protein chain wherein the linker is long enough to allow the protein chain to fold back on itself and form a monovalent antigen binding site

25 (see, *e.g.*, Bird *et al.*, 1988, Science 242:423-26 and Huston *et al.*, 1988, Proc. Natl. Acad. Sci. USA 85:5879-83). Diabodies are bivalent antibodies comprising two polypeptide chains, wherein each polypeptide chain comprises V_H and V_L domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (see, *e.g.*, Holliger *et al.*, 1993, Proc. Natl. Acad. Sci. USA 90:6444-48, and

30 Poljak *et al.*, 1994, Structure 2:1121-23). If the two polypeptide chains of a diabody are identical, then a diabody resulting from their pairing will have two identical antigen binding sites. Polypeptide chains having different sequences can be used to make a diabody with two different antigen binding sites. Similarly, tribodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or

35 different.

Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody may be identified using the system described by Kabat *et al.* in Sequences of Proteins of Immunological Interest, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no: 91-3242, 1991. One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an

40 antigen binding protein. An antigen binding protein may incorporate the CDR(s) as part of a larger

polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the antigen binding protein to specifically bind to a particular antigen of interest.

An antigen binding protein may have one or more binding sites. If there is more than one binding
5   site, the binding sites may be identical to one another or may be different. For example, a naturally occurring human immunoglobulin typically has two identical binding sites, while a "bispecific" or "bifunctional" antibody has two different binding sites.

The term "human antibody" includes all antibodies that have one or more variable and constant regions derived from human immunoglobulin sequences. In one embodiment, all of the variable and
10   constant domains are derived from human immunoglobulin sequences (a fully human antibody). These antibodies may be prepared in a variety of ways, examples of which are described below, including through the immunization with an antigen of interest of a mouse that is genetically modified to express antibodies derived from human heavy and/or light chain-encoding genes.

A humanized antibody has a sequence that differs from the sequence of an antibody derived from a
15   non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In one embodiment, certain amino acids in the framework and constant domains of the heavy and/or light chains of the non-human species antibody are mutated to produce the humanized antibody. In another
20   embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific binding of the antibody to its antigen, or the changes to the amino acid sequence that are
25   made are conservative changes, such that the binding of the humanized antibody to the antigen is not significantly worse than the binding of the non-human antibody to the antigen. Examples of how to make humanized antibodies may be found in U.S. Pat. Nos. 6,054,297, 5,886,152 and 5,877,293.

The term "chimeric antibody" refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. In one embodiment, one or more of
30   the CDRs are derived from a human anti-IGF-1R antibody. In another embodiment, all of the CDRs are derived from a human anti-IGF-1R antibody. In another embodiment, the CDRs from more than one human anti-IGF-1R antibodies are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first human anti-IGF-1R antibody, a CDR2 and a CDR3 from the light chain of a second human anti-IGF-1R antibody, and the CDRs from the heavy chain
35   from a third anti-IGF-1R antibody. Further, the framework regions may be derived from one of the same anti-IGF-1R antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. In one example of a chimeric antibody, a portion of the heavy and/or light chain is identical with, homologous to, or derived from an antibody from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with, homologous
40   to, or derived from an antibody (-ies) from another species or belonging to another antibody class or

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subclass. Also included are fragments of such antibodies that exhibit the desired biological activity (*i.e.*, the ability to specifically bind IGF-1R). See, *e.g.*, U.S. Patent No. 4,816,567 and Morrison, 1985, Science 229:1202-07.

5   A "neutralizing antibody" or "an inhibitory antibody" is an antibody that inhibits the binding of IGF-1R to IGF-I and/or IGF-2 when an excess of the anti-IGF-1R antibody reduces the amount of IGF-I and/or IGF-2 bound to IGF-1R by at least about 20% using the assay described in Example 9. In various embodiments, the antibody reduces the amount of IGF-I and/or IGF-2 bound to IGF-1R by at least 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, and 99.9%.

          An "activating antibody" is an antibody that activates IGF-1R by at least about 20% when added to

10   a cell, tissue or organism expressing IGF-1R, where "100% activation" is the level of activation achieved under physiological conditions by the same molar amount of IGF-1 and/or IGF-2. In various embodiments, the antibody activates IGF-1R activity by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 750%, or 1000%.

          Fragments or analogs of antibodies can be readily prepared by those of ordinary skill in the art

15   following the teachings of this specification and using techniques well-known in the art. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Computerized comparison methods can be used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure

20   and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. See, *e.g.*, Bowie *et al.*, 1991, Science 253:164.

          A "CDR grafted antibody" is an antibody comprising one or more CDRs derived from an antibody of a particular species or isotype and the framework of another antibody of the same or different species or isotype.

25   A "multi-specific antibody" is an antibody that recognizes more than one epitope on one or more antigens. A subclass of this type of antibody is a "bi-specific antibody" which recognizes two distinct epitopes on the same or different antigens.

          An antigen binding protein "specifically binds" to an antigen (*e.g.*, human IGF-1R) if it binds to the antigen with a dissociation constant of 1 nanomolar or less.

30   An "antigen binding domain," "antigen binding region," or "antigen binding site" is a portion of an antigen binding protein that contains amino acid residues (or other moieties) that interact with an antigen and contribute to the antigen binding protein's specificity and affinity for the antigen. For an antibody that specifically binds to its antigen, this will include at least part of at least one of its CDR domains.

          An "epitope" is the portion of a molecule that is bound by an antigen binding protein (e.g., by an

35   antibody). An epitope can comprise non-contiguous portions of the molecule (*e.g.*, in a polypeptide, amino acid residues that are not contiguous in the polypeptide's primary sequence but that, in the context of the polypeptide's tertiary and quaternary structure, are near enough to each other to be bound by an antigen binding protein).

The "percent identity" of two polynucleotide or two polypeptide sequences is determined by comparing the sequences using the GAP computer program (a part of the GCG Wisconsin Package, version 10.3 (Accelrys, San Diego, CA)) using its default parameters.

The terms "polynucleotide," "oligonucleotide" and "nucleic acid" are used interchangeably

5   throughout and include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), analogs of the DNA or RNA generated using nucleotide analogs (*e.g.*, peptide nucleic acids and non-naturally occurring nucleotide analogs), and hybrids thereof. The nucleic acid molecule can be single-stranded or double-stranded. In one embodiment, the nucleic acid molecules of the invention comprise a contiguous open reading frame encoding an antibody, or a fragment, derivative, mutein, or variant thereof,

10   of the invention.

Two single-stranded polynucleotides are "the complement" of each other if their sequences can be aligned in an anti-parallel orientiation such that every nucleotide in one polynucleotide is opposite its complementary nucleotide in the other polynucleotide, without the introduction of gaps, and without unpaired nucleotides at the 5' or the 3' end of either sequence. A polynucleotide is "complementary" to

15   another polynucleotide if the two polynucleotides can hybridize to one another under moderately stringent conditions. Thus, a polynucleotide can be complementary to another polynucleotide without being its complement.

A "vector" is a nucleic acid that can be used to introduce another nucleic acid linked to it into a cell. One type of vector is a "plasmid," which refers to a linear or circular double stranded DNA molecule

20   into which additional nucleic acid segments can be ligated. Another type of vector is a viral vector (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), wherein additional DNA segments can be introduced into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors comprising a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated

25   into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. An "expression vector" is a type of vector that can direct the expression of a chosen polynucleotide.

A nucleotide sequence is "operably linked" to a regulatory sequence if the regulatory sequence affects the expression (*e.g.*, the level, timing, or location of expression) of the nucleotide sequence. A

30   "regulatory sequence" is a nucleic acid that affects the expression (*e.g.*, the level, timing, or location of expression) of a nucleic acid to which it is operably linked. The regulatory sequence can, for example, exert its effects directly on the regulated nucleic acid, or through the action of one or more other molecules (*e.g.*, polypeptides that bind to the regulatory sequence and/or the nucleic acid). Examples of regulatory sequences include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation

35   signals). Further examples of regulatory sequences are described in, for example, Goeddel, 1990, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, CA and Baron *et al.*, 1995, Nucleic Acids Res. 23:3605–06.

A "host cell" is a cell that can be used to express a nucleic acid, *e.g.*, a nucleic acid of the invention. A host cell can be a prokaryote, for example, *E. coli*, or it can be a eukaryote, for example, a

40   single-celled eukaryote (*e.g.*, a yeast or other fungus), a plant cell (*e.g.*, a tobacco or tomato plant cell), an

animal cell (*e.g.*, a human cell, a monkey cell, a hamster cell, a rat cell, a mouse cell, or an insect cell) or a hybridoma. Examples of host cells include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (see Gluzman *et al.*, 1981, Cell 23:175), L cells, C127 cells, 3T3 cells (ATCC CCL 163), Chinese hamster ovary (CHO) cells or their derivatives such as Veggie CHO and related cell lines which grow in serum-free media

5   (see Rasmussen *et al.*, 1998, Cytotechnology 28:31) or CHO strain DX-B11, which is deficient in DHFR (see Urlaub *et al.*, 1980, Proc. Natl. Acad. Sci. USA 77:4216-20), HeLa cells, BHK (ATCC CRL 10) cell lines, the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) (see McMahan *et al.*, 1991, EMBO J. 10:2821), human embryonic kidney cells such as 293, 293 EBNA or MSR 293, human epidermal A431 cells, human Colo205 cells, other transformed primate cell lines,

10   normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HL-60, U937, HaK or Jurkat cells. Typically, a host cell is a cultured cell that can be transformed or transfected with a polypeptide-encoding nucleic acid, which can then be expressed in the host cell. The phrase "recombinant host cell" can be used to denote a host cell that has been transformed or transfected with a nucleic acid to be expressed. A host cell also can be a cell that comprises the nucleic acid but does not

15   express it at a desired level unless a regulatory sequence is introduced into the host cell such that it becomes operably linked with the nucleic acid. It is understood that the term host cell refers not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to, *e.g.*, mutation or environmental influence, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

20

IGF-1R

IGF-1R is a transmembrane receptor tyrosine kinase (Blume-Jensen *et al.*, 2001, Nature 411:355-65). The human IGF-1R is synthesized as a 1367 amino acid precursor polypeptide that includes a 30 amino acid signal peptide removed during translocation into the endoplasmic reticulum (Swiss-Prot:

25   P08069). The IGF-1R proreceptor is glycosylated and cleaved by a protease at positions 708-711 (counting from the first amino acid following the signal peptide sequence) during maturation in the ER-golgi resulting in the formation of an α-chain (1-707) and a β-chain (712-1337) that remain linked by disulfide bonds (Bhaumick *et al.*, 1981, Proc Natl Acad Sci USA 78:4279-83, Chernausek *et al.*, 1981, Biochemistry 20:7345-50, Jacobs *et al.*, 1983, Proc Natl Acad Sci USA 80:1228-31, LeBon *et al.*, 1986, J Biol Chem

30   261:7685-89, Elleman, *et al.*, 2000, Biochem J 347:771-79). The predominant form of the IGF-1R (and INSR) that exists on the cell-surface is a proteolytically processed and glycosylated $(\alpha\beta)_2$ dimer joined covalently by one or more disulfide bonds.

The extracellular portion of the IGF-1R consists of the α-chain and 191 amino acids of the β-chain (712-905). The receptor contains a single transmembrane spanning sequence (906-929) and a 408-residue

35   cytoplasmic domain that includes a functional tyrosine kinase (Rubin *et al.*, 1983, Nature 305:438-440). Comparative sequence analysis has revealed that the IGF-1R is composed of 11 distinct structural motifs (reviewed by Adams *et al.*, 2000, Cell Mol Life Sci 57:1050-93, Marino-Buslje *et al.*, 1998, FEBS Ltrs 441:331-36, Ward *et al.*, 2001, BMC Bioinformatics 2:4). The N-terminal half of the extracellular domain contains two homologous domains referred to as L1 (1-151) and L2 (299-461) (Ward *et al.*, 2001, *supra*)

40   separated by a cysteine-rich (CR) region (152-298) consisting of several structural modules with disulfide

linkages that align with repeating units present in the TNF receptor and laminin (Ward *et al.*, 1995, Proteins 22:141-53). The crystal structure of the L1—CR-L2 domain has been solved (Garrett *et al.*, 1998, Nature 394:395-99). The L2 domain is followed by three fibronectin type III domains (Marino-Buslje *et al.*, 1998, *supra*, Mulhern *et al.*, 1998, Trends Biochem Sci 23:465-66, Ward *et al.*, 1999, Growth Factors 16:315-22).

5 The first FnIII domain (FnIII-1, 461-579) is 118 amino acids in length. The second FnIII domain (FnIII-2, 580-798) is disrupted by a major insert sequence (ID) of about 120 amino acids in length. The ID domain includes a furin protease cleavage site that separates the α and β chains of the mature receptor. The third FnIII domain (FnIII-3) is located entirely in the β-chain (799-901) terminating several residues before the transmembrane sequence. The catalytic domain of the IGF-1R tyrosine kinase is located between amino

10 acids positions 973-1229, and its structure has been solved (Favelyukis *et al.*, 2001, Nature Structural Biol 8:1058-63, Pautsch *et al.*, 2001, Structure 9:955-65). The kinase is flanked by two regulatory regions, the juxtamembrane region (930-972) and a 108 amino acid C-terminal tail (1220-1337) (Surmacz *et al.*, 1995, Experimental Cell Res 218:370-80, Hongo *et al.*, 1996, Oncogene 12:1231-38). The two regulatory regions contain tyrosine residues that serve as docking sites for signal transducing proteins when phosphorylated by

15 the activated IGF-1R tyrosine kinase (reviewed by Baserga (ed.), 1998 *The IGF-1 Receptor in Normal and Abnormal Growth*, Hormones and Growth Factors in Development and Neoplasia, Wiley-Liss, Inc., Adams *et al.*, 2000, Cell Mol Life Sci 57:1050-93).

The IGF-1R amino acid sequence is about 70% identical to the insulin receptor (INSR; Swiss-Prot: P06213). The highest homology between the receptors is located in the tyrosine kinase domain (84%); the

20 lowest identity is in the CR region and the C-terminus. The IGF-1R is also highly related (~ 55% identical) to the insulin related receptor (IRR; Swiss-Prot: P14616).

Human IGF-1R can be activated by the insulin-like growth factors, IGF-1 and IGF-2 and insulin (INS) (Hill *et al.*, 1985, Pediatric Research 19:879-86). IGF-1 and IGF-2 are encoded nonallelic genes (Brissenden *et al.*, 1984, Nature 310: 781-8, Bell *et al.*, 1985, Proceedings of the National Academy of

25 Sciences of the United States of America 82: 6450-54), and both genes express alternative proteins related by differential RNA splicing and protein processing. The most common and well-studied mature forms of IGF-1 and IGF-2 are respectively 70 and 67 amino acids in length (Jansen *et al.*, 1983, Nature 306:609-11, Dull *et al.*, 1984, Nature 310: 777-81). These proteins (and their isoforms) are identical at 11/21 positions to the insulin A-peptide, and identical at 12/30 positions with the insulin B-peptide.

30 IGF-1R is expressed in all cells types in the normal adult animal except for liver hepatocytes and mature B-cells. Human blood plasma contains high concentrations of IGF-1 and IGF-2, and IGF-1 can be detected in most tissues. The receptor is an integral component of the physiological mechanism controlling organ size and homeostasis. Without being bound to a particular theory, the "Somatomedin Hypothesis" states that Growth Hormone (GH) mediated somatic growth that occurs during childhood and adolescence

35 is dependent on the endocrine form of IGF-1 that is mainly produced and secreted by the liver (Daughaday, 2000, Pediatric Nephrology 14: 537-40). The synthesis of hepatic IGF-1 is stimulated by GH release in the pituitary in response to hypothalamic GHRH (GH releasing hormone). The serum concentration of IGF-1 increases over 100 fold between ages 5-15 in humans. The bioavailability of IGF-1 is regulated by IGF binding protein 3 (IGFBP3) with approximately 99% of the growth factor compartmentalized in the bound

40 state. Primary IGF-1 deficiency arising form partial gene deletions, and secondary IGF-1 deficiency

resulting from defects in GH production or signaling are not lethal (Woods, 1999, *IGF Deficiency* in Contemporary Endocrinology: The IGF System, R. a. R. Rosenfeld, C. Jr. Totowa, ed.s, Humana Press, NJ: 651-74). The affected individuals exhibit growth retardation at birth, grow slowly and can face certain CNS abnormalities.

5   IGF-1R signaling promotes cell growth and survival through the IRS adapter protein-dependent activation of the PI3Kinase/Akt pathway. IGF-1R transmits a signal to its major substrates, IRS-1 through IRS-4 and the Shc proteins (Blakesley *et al.*, 1999, *IGF-1 receptor function: transducing the IGF-1 signal into intracellular events* in The IGF System, R. G. a. R. Rosenfeld, Jr. C.T. Totowa, ed.s, Humana Press, NJ: 143-63). This results in activation of the Ras/Raf/MAP kinase and PI3 Kinase/Akt signaling pathways.

10   However, induction of Akt-mediated cell survival via IRS is the dominant pathway response upon IGF stimulation of most cells. See Figure 10.

Antigen binding proteins

        In one aspect, the present invention provides antigen binding proteins (*e.g.*, antibodies, antibody

15   fragments, antibody derivatives, antibody muteins, and antibody variants), that bind to IGF-1R, *e.g.*, human IGF-1R.

        Antigen binding proteins in accordance with the present invention include antigen binding proteins that inhibit a biological activity of IGF-1R. Examples of such biological activities include binding a signaling molecule (*e.g.*, IGF-1 and/or IGF-2), and transducing a signal in response to binding a signaling

20   molecule.

        Different antigen binding proteins may bind to different domains or epitopes of IGF-1R or act by different mechanisms of action. Examples include but are not limited to antigen binding proteins that interfere with binding of IGF-1 and/or IGF-2 to IGF-1R or that inhibit signal transduction. The site of action may be, for example, intracellular (*e.g.*, by interfering with an intracellular signaling cascade) or

25   extracellular. An antigen binding protein need not completely inhibit an IGF-1 and/or IGF-2 induced activity to find use in the present invention; rather, antigen binding proteins that reduce a particular activity of IGF-1 and/or IGF-2 are contemplated for use as well. (Discussions herein of particular mechanisms of action for IGF-1R-binding antigen binding proteins in treating particular diseases are illustrative only, and the methods presented herein are not bound thereby.)

30   It has been observed that IGF-1 and IGF-2 each exhibits biphasic binding to IGF-1R. High affinity binding has been reported to have a K_D in the range of 0.2 nM; high affinity binding, about ten fold higher. Thus, in one embodiment, the present invention provides an IGF-1R inhibitor that inhibits both the high and low affinity binding of IGF-1 and/or IGF-2 to IGF-R. It has been suggested that the high affinity binding, rather than the low affinity binding, of IGF-1 and/or IGF-2 to IGF-1R is required for the conformation

35   change that activates the tyrosine kinase activity of IGF-1R. Thus, in another embodiment, the IGF-1R inhibitor preferentially inhibits the high affinity binding of IGF-1 and/or IGF-2 to IGF-1R as compared to the low affinity binding.

        In another aspect, the present invention provides antigen binding proteins that comprise a light chain variable region selected from the group consisting of L1 through L52 and/or a heavy chain variable

40   region selected from the group consisting of H1 through H52, and fragments, derivatives, muteins, and

variants thereof (see Figures 2 and 3). Such an antigen binding protein can be denoted using the nomenclature "LxHy", wherein "x" corresponds to the number of the light chain variable region and "y" corresponds to the number of the heavy chain variable region as they are labeled in Figures 2 and 3. For example, L2H1 refers to an antigen binding protein with a light chain variable region comprising the amino

5   acid sequence of L2 and a heavy chain variable region comprising the amino acid sequence of H1, as shown in Figures 2 and 3. Figures 2 and 3 also indicate the location of the CDR and framework regions of each of these variable domain sequences. The CDR regions of each light and heavy chain also are grouped by type and by sequence similarity in Figures 4 through 9. Antigen binding proteins of the invention include, for example, antigen binding proteins having a combination of light chain and heavy chain variable domains

10   selected from the group of combinations consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51,

15   and L52H52.

        In one embodiment, the present invention provides an antigen binding protein comprising a light chain variable domain comprising a sequence of amino acids that differs from the sequence of a light chain variable domain selected from the group consisting of L1 through L52 only at 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 residues, wherein each such sequence difference is independently either a deletion,

20   insertion, or substitution of one amino acid residue. In another embodiment, the light-chain variable domain comprises a sequence of amino acids that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to the sequence of a light chain variable domain selected from the group consisting of L1 through L52. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is . encoded by a nucleotide sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical

25   to a nucleotide sequence that encodes a light chain variable domain selected from the group consisting of L1 through L52. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide that encodes a light chain variable domain selected from the group consisting of L1 through L52. In another embodiment, the light chain variable domain comprises a

30   sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide that encodes a light chain variable domain selected from the group consisting of L1 through L52. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to a complement of a light chain polynucleotide selected from Figure 1.

35   In another embodiment, the present invention provides an antigen binding protein comprising a heavy chain variable domain comprising a sequence of amino acids that differs from the sequence of a heavy chain variable domain selected from the group consisting of H1 through H52 only at 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 residue(s), wherein each such sequence difference is independently either a deletion, insertion, or substitution of one amino acid residue. In another embodiment, the heavy chain

40   variable domain comprises a sequence of amino acids that is at least 70%, 75%, 80%, 85%, 90%, 95%,

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97%, or 99% identical to the sequence of a heavy chain variable domain selected from the group consisting of H1 through H52. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a nucleotide sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to a nucleotide sequence that encodes a heavy chain variable domain selected from

5   the group consisting of H1 through H52. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide that encodes a heavy chain variable domain selected from the group consisting of H1 through H52. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under

10   moderately stringent conditions to the complement of a polynucleotide that encodes a heavy chain variable domain selected from the group consisting of H1 through H52. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to a complement of a heavy chain polynucleotide selected from Figure 1.

15   Particular embodiments of antigen binding proteins of the present invention comprise one or more amino acid sequences that are identical to the amino acid sequences of one or more of the CDRs and/or FRs illustrated in Figures 2 through 9. In one embodiment, the antigen binding protein comprises a light chain ·CDR1 sequence illustrated in Figure 4. In another embodiment, the antigen binding protein comprises a light chain CDR2 sequence illustrated in Figure 5. In another embodiment, the antigen binding protein

20   comprises a light chain CDR3 sequence illustrated in Figure 6. In another embodiment, the antigen binding protein comprises a heavy chain CDR1 sequence illustrated in Figure 7. In another embodiment, the antigen binding protein comprises a heavy chain CDR2 sequence illustrated in Figure 8. In another embodiment, the antigen binding protein comprises a heavy chain CDR3 sequence illustrated in Figure 9. In another embodiment, the antigen binding protein comprises a light chain FR1 sequence illustrated in

25   Figure 2. In another embodiment, the antigen binding protein comprises a light chain FR2 sequence illustrated in Figure 2. In another embodiment, the antigen binding protein comprises a light chain FR3 sequence illustrated in Figure 2. In another embodiment, the antigen binding protein comprises a light chain FR4 sequence illustrated in Figure 2. In another embodiment, the antigen binding protein comprises a heavy chain FR1 sequence illustrated in Figure 3. In another embodiment, the antigen binding protein

30   comprises a heavy chain FR2 sequence illustrated in Figure 3. In another embodiment, the antigen binding protein comprises a heavy chain FR3 sequence illustrated in Figure 3. In another embodiment, the antigen binding protein comprises a heavy chain FR4 sequence illustrated in Figure 3.

In one embodiment, the present invention provides an antigen binding protein that comprises one or more CDR sequences that differ from a CDR sequence shown in Figures 2 through 9 by no more than 5,

35   4, 3, 2, or 1 amino acid residues.

In one embodiment, the present invention provides an antigen binding protein that comprises at least one CDR from L1-L52 and/or H1-H52, as shown in Figures 2 through 9, and at least one CDR sequence from an anti-IGF-1R antibody described in US Pat. App. Pub. Nos. 03/0235582, 04/0228859, 04/0265307, 04/0886503, 05/0008642, 05/0084906, 05/0186203, 05/0244408, PCT Pub. Nos. WO

40   03/059951, WO 03/100008, WO 04/071529A2, WO 04/083248, WO 04/087756, WO 05/016967, WO

05/016970, or WO 05/058967 (each of which is incorporated herein by reference in its entirety for all purposes) wherein the antigen binding protein binds to IGF-1 receptor. In another embodiment, the antigen binding protein comprises 2, 3, 4, or 5 CDR sequences from L1-L52 and/or H1-H52, as shown in Figures 2 through 9. In another embodiment, the antigen binding protein comprises 2, 3, 4, or 5 CDR sequences from

5   an anti-IGF-1R antibody described in US Pat. App. Pub. Nos. 03/0235582, 04/0228859, 04/0265307, 04/0886503, 05/0008642, 05/0084906, 05/0186203, 05/0244408, PCT Pub. Nos. WO 03/059951, WO 03/100008, WO 04/071529A2, WO 04/083248, WO 04/087756, WO 05/016967, WO 05/016970, or WO 05/058967. In another embodiment, at least one of the antigen binding protein's CDR3 sequences is a CDR3 sequence from L1-L52 and/or H1-H52, as shown in Figures 2, 3, 6, and 9. In another embodiment,

10   the antigen binding protein's light chain CDR3 sequence is a light chain CDR3 sequence from L1-L52 as shown in Figures 2 and 6 and the antigen binding protein's heavy chain CDR3 sequence is a heavy chain sequence from H1-H52 as shown in Figures 3 and 9. In another embodiment, the antigen binding protein comprises 1, 2, 3, 4, or 5 CDR sequences that each independently differs by 6, 5, 4, 3, 2, 1, or 0 single amino acid additions, substitutions, and/or deletions from a CDR sequence of L1-L52 and/or H1-H52, and

15   the antigen binding protein further comprises 1, 2, 3, 4, or 5 CDR sequences that each independently differs by 6, 5, 4, 3, 2, 1, or 0 single amino acid additions, substitutions, and/or deletions from a CDR sequence of US Pat. App. Pub. Nos. 03/0235582, 04/0228859, 04/0265307, 04/0886503, 05/0008642, 05/0084906, 05/0186203, 05/0244408, PCT Pub. Nos. WO 03/059951, WO 03/100008, WO 04/071529A2, WO 04/083248, WO 04/087756, WO 05/016967, WO 05/016970, or WO 05/058967. In another embodiment,

20   the CDR sequence(s) from US Pat. App. Pub. Nos. 03/0235582, 04/0228859, 04/0265307, 04/0886503, 05/0008642, 05/0084906, 05/0186203, 05/0244408, PCT Pub. Nos. WO 03/059951, WO 03/100008, WO 04/071529A2, WO 04/083248, WO 04/087756, WO 05/016967, WO 05/016970, or WO 05/058967. In another embodiment, the CDR sequence(s) are from (an) antibody(-ies) that bind(s) to the L2 portion of the extracellular domain of IGF-1 receptor. In another embodiment, the antigen binding protein does not

25   comprise a light chain CDR3 sequence and/or a heavy chain CDR3 sequence from an anti-IGF-1R antibody from US Pat. App. Pub. Nos. 03/0235582, 04/0228859, 04/0265307, 04/0886503, 05/0008642, 05/0084906, 05/0186203, 05/0244408, PCT Pub. Nos. WO 03/059951, WO 03/100008, WO 04/071529A2, WO 04/083248, WO 04/087756, WO 05/016967, WO 05/016970, or WO 05/058967.

In one embodiment, the present invention provides an antigen binding protein that comprises a

30   light chain CDR1 comprising the sequence RSSQSLLHX$_1$X$_2$GYNX$_3$LX$_4$ (SEQ ID NO:236), wherein X$_1$ is a serine or a threonine residue, X$_2$ is an asparagine, serine, or histidine residue, X$_3$ is a tyrosine or a phenylalanine residue, and X$_4$ is an aspartate or an asparagine residue. In another embodiment, the light chain CDR1 comprises the sequence TRSSGX$_1$IX$_2$X$_3$NYVQ (SEQ ID NO:237), wherein X$_1$ is a serine or an aspartate residue, X$_2$ is an alanine or an aspartate residue, and X$_3$ is a serine or an asparagine residue. In

35   another embodiment, the light chain CDR1 comprises the sequence RASQX$_1$X$_2$X$_3$X$_4$X$_5$LX$_6$ (SEQ ID NO:238), wherein X$_1$ is a glycine or a serine residue, X$_2$ is an isoleucine, valine, or proline residue, and X$_3$ is a serine, glycine, or tyrosine residue, X$_4$ is any amino acid residue, X$_5$ is a phenylalanine, tyrosine, asparagine, or tryptophan residue, and X$_6$ is an alanine or an asparagine residue. In another embodiment, X$_2$ is an isoleucine or valine residue, X$_3$ is a glycine or serine residue, X$_4$ is an arginine, serine, asparagine,

40   serine, tyrosine, or isoleucine residue, and X$_5$ is a phenylalanine or a tyrosine residue.

In one embodiment, the present invention provides an antigen binding protein that comprises a light chain CDR2 comprising the sequence $LX_1X_2X_3RX_4S$ (SEQ ID NO:239), wherein X_1 is a glycine or a valine residue, X_2 is a serine or a phenylalanine residue, X_3 is an asparagine, tyrosine, or threonine residue, and X_4 is an alanine or an aspartate residue. In another embodiment, the CDR2 comprises the sequence $AX_1SX_2LX_3S$ (SEQ ID NO:240), wherein X_1 is an alanine or a threonine residue, X_2 is a threonine or a glycine residue, and X_3 is a glutamine or a glutamate residue. In another embodiment, the CDR2 comprises the sequence $X_1X_2NX_3RPS$ (SEQ ID NO:241), wherein X_1 is a glutamate, glutamine, or glycine residue, X_2 is an aspartate or lysine residue, and X_3 is any amino acid residue.

In one embodiment, the present invention provides an antigen binding protein that comprises a light chain CDR3 comprising the sequence $MX_1X_2X_3X_4X_5PX_6X_7$ (SEQ ID NO:242), wherein X_1 is a glutamine or glutamate residue, X_2 is an alanine, glycine, serine, or threonine residue, X_3 is a leucine or threonine residue, X_4 is a glutamine, glutamate, or histidine residue, X_5 is a threonine, tryptophan, methionine, or valine residue, X_6 is a nonpolar side chain residue, and X_7 is a threonine, serine, or alanine residue. In another embodiment, the CDR3 comprises the sequence $QQX_1X_2X_3X_4PX_5T$ (SEQ ID NO:243), wherein X_1 is an arginine, serine, leucine, or alanine residue, X_2 is an asparagine, serine, or histidine residue, X_3 is a serine or an asparagine residue, X_4 is a nonpolar side chain residue, and X_5 is a leucine, isoleucine, tyrosine, or tryptophan residue. In another embodiment, the CDR3 comprises the sequence $QSYX_1SX_2NX_3X_4V$ (SEQ ID NO:244), wherein X_1 is an aspartate or a glutamine residue, X_2 is a serine or an aspartate residue, X_3 is a glutamine, valine, or tryptophan residue, and X_4 is an arginine residue or no residue.

In one embodiment, the present invention provides an antigen binding protein that comprises a heavy chain CDR1 comprising the sequence $X_1X_2X_3WWS$ (SEQ ID NO:245), wherein X_1 is a serine residue or no residue, X_2 is a serine or asparagine residue, and X_3 is an asparagine residue and an isoleucine residue. In another embodiment, the heavy chain CDR1 comprises the sequence X_1X_2YWS (SEQ ID NO:246), wherein X_1 is a glycine, asparagine, or aspartate residue, and X_2 is a tyrosine or phenylalanine residue. In another embodiment, the heavy chain CDR1 comprises the sequence $SYX_1X_2X_3$ (SEQ ID NO:247), wherein X_1 is an alanine or glycine residue, X_2 is a methionine or isoleucine residue, and X_3 is a serine or histidine residue.

In one embodiment, the present invention provides an antigen binding protein that comprises a heavy chain CDR2 comprising the sequence $X_1X_2X_3X_4X_5GX_6TX_7YNPSLX_8S$ (SEQ ID NO:248), wherein X_1 is a glutamate, tyrosine, or serine residue, X_2 is a isoleucine or valine residue, X_3 is a tyrosine, asparagine, or serine residue, X_4 is a histidine, tyrosine, aspartate, or proline residue, X_5 is a serine or arginine residue, X_6 is a serine or asparagine residue, X_7 is an asparagine or tyrosine residue, and X_8 is a lysine or glutamate residue. In another embodiment, the heavy chain CDR2 comprises the sequence $X_1ISX_2X_3X_4X_5X_6X_7YYADSVKG$ (SEQ ID NO:249), wherein X_1 is a threonine, alanine, valine, or tyrosine residue, X_2 is a glycine, serine, or tyrosine residue, X_3 is a serine, asparagine, or aspartate residue, X_4 is a glycine or serine residue, X_5 is a glycine, serine, or aspartate residue, X_6 is a serine, threonine, or asparagine residue, and X_7 is a threonine, lysine, or isoleucine residue.

In one embodiment, the present invention provides an antigen binding protein that comprises a heavy chain CDR3 comprising the sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9FDI$ (SEQ ID NO:250), wherein X_1 is a

glutamate residue or no residue, X_2 is tyrosine, glycine, or serine residue or no residue, X_3 is a serine, asparagine, tryptophan, or glutamate residue, or no residue, X_4 is a serine, aspartate, tryptophan, alanine, arginine, threonine, glutamine, leucine, or glutamate residue, or no residue, X_5 is a serine, glycine, asparagine, threonine, tryptophan, alanine, valine, or isoleucine residue, X_6 is an arginine, glutamine,

5   tyrosine, valine, alanine, glycine, serine, phenylalanine, or tryptophan residue, X_7 is a leucine, asparagine, aspartate, threonine, tryptophan, tyrosine, valine, alanine, or histidine residue, X_8 is an aspartate, serine, asparagine, or glutamine residue, and X_9 is an alanine or a proline residue. In another embodiment, the heavy chain CDR3 comprises the sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}MDV$ (SEQ ID NO:251), wherein X_1 is an alanine residue, or no residue, X_2 is a glutamate, tyrosine, or glycine residue, or no residue,

10   X_3 is a serine or arginine residue, or no residue, X_4 is an aspartate, glycine, serine, or valine residue, or no residue, X_5 is a serine, glycine, or aspartate residue, or no residue, X_6 is a glycine, phenylalanine, aspartate, serine, tryptophan, or tyrosine residue, or no residue, X_7 is a tyrosine, tryptophan, serine, or aspartate residue, or no residue, X_8 is an aspartate, arginine, serine, glycine, tyrosine, or tryptophan residue, X_9 is a tyrosine, isoleucine, leucine, phenylalanine, or lysine residue, X_{10} is a tyrosine, phenylalanine, aspartate, or

15   glycine residue, and X_{11} is a glycine, tyrosine, or asparagine residue. In another embodiment, the heavy chain CDR3 comprises the sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}Y$ (SEQ ID NO:252), wherein X_1 is an aspartate or valine residue, or no residue, X_2 is a glycine, tyrosine, arginine, or aspartate residue, or no residue, X_3 is an asparagine, leucine, glycine, isoleucine, serine, valine, phenylalanine, or tyrosine residue, or no residue, X_4 is a leucine, serine, tryptophan, alanine, tyrosine, isoleucine, glycine, or aspartate residue,

20   or no residue, X_5 is a glycine, alanine, tyrosine, serine, aspartate, or leucine residue, X_6 is a valine, alanine, glycine, threonine, proline, histidine, or glutamine residue, X_7 is a glutamate, glycine, serine, aspartate, glycine, valine, tryptophan, histidine, or arginine residue, X_8 is a glutamine, alanine, glycine, tyrosine, proline, leucine, aspartate, or serine residue, X_9 is a nonpolar side chain residue, and X_{10} is an aspartate or alanine residue. In another embodiment, the heavy chain CDR3 comprises the sequence

25     $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}YFDX_{11}$ (SEQ ID NO:253), wherein X_1 is a glycine residue, or no residue, X_2 is a proline residue, or no residue, X_3 is an arginine or aspartate residue, or no residue, X_4 is a histidine or proline residue, X_5 is an arginine or glycine residue, X_6 is an arginine, serine, or phenylalanine residue, X_7 is an aspartate or serine residue, X_8 is a glycine, tryptophan, or tyrosine residue, X_9 is a tyrosine or alanine residue, X_{10} is an asparagine or tryptophan residue, and X_{11} is an asparagine or leucine residue. In another

30   embodiment, the heavy chain CDR3 comprises the sequence $X_1X_2X_3X_4DSSX_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO:254), wherein X_1 is a phenylalanine residue, or no residue, X_2 is an asparagine or glycine residue, or no residue, X_3 is a tyrosine or a leucine residue, or no residue, X_4 is a tyrosine or glycine residue, or no residue, X_5 is a glycine, serine, or valine residue, X_6 is a tyrosine, phenylalanine, tryptophan, or glutamine residue, or no residue, X_7 is a tyrosine, glycine, or isoleucine residue, or no residue, X_8 is a tyrosine,

35   leucine, or glycine residue, or no residue, X_9 is a methionine, glycine, or phenylalanine residue, or no residue, X_{10} is an aspartate or methionine residue, or no residue, X_{11} is a valine, aspartate, or tyrosine residue, or no residue, and X_{12} is a valine residue, or no residue.

        In one embodiment, the present invention provides an isolated antigen binding protein, comprising either: a. a light chain CDR3 comprising a sequence selected from the group consisting of: i. a light chain

40   CDR3 sequence selected from the group consisting of the light chain CDR3 sequences of L1-L52 as shown

in Figure 6; ii. MQALQTPZT; iii. QQ(R/S)(N/S)(S/N)ZPLT; and iv. QSYDSSNXJV; b. a heavy chain

CDR3 comprising a sequence selected from the group consisting of: i. a heavy chain CDR3 sequence that

differs by no more than a total of three amino acid additions, substitutions, or deletions from a CDR3

sequence selected from the group consisting of the heavy chain CDR3 sequences of H1-H52 as shown in

5   Figure 9; ii. SRLDAFDI; iii. SXYDYYGMDV; iv. HRXDXAWYFDL; and v. DSSG; or c. the light

chain CDR3 sequence of (a) and the heavy chain CDR3 sequence of (b); wherein amino acid residue

symbols enclosed in parentheses identify alternative residues for the same position in a sequence, each X is

independently any amino acid residue, each Z is independently a glycine residue, an alanine residue, a

valine residue, a leucine residue, an isoleucine residue, a proline residue, a phenylalanine residue, a

10   methionine residue, a tryptophan residue, or a cysteine residue, each J is independently a glutamine residue,

an arginine residue, a valine residue, or a tryptophan residue, and the antigen binding protein binds to

human IGF-1R.

        The nucleotide sequences of Figure 1, or the amino acid sequences of Figures 2 through 9, can be

altered, for example, by random mutagenesis or by site-directed mutagenesis (e.g., oligonucleotide-directed

15   site-specific mutagenesis) to create an altered polynucleotide comprising one or more particular nucleotide

substitutions, deletions, or insertions as compared to the non-mutated polynucleotide. Examples of

techniques for making such alterations are described in Walder et al., 1986,Gene 42:133; Bauer et al.1985,

Gene 37:73; Craik, BioTechniques, January 1985, 12-19; Smith et al., 1981, *Genetic Engineering:*

Principles and Methods, Plenum Press; and U.S. Patent Nos. 4,518,584 and 4,737,462. These and other

20   methods can be used to make, for example, derivatives of anti-IGF-1R antibodies that have a desired

property, for example, increased affinity, avidity, or specificity for IGF-1R, increased activity or stability *in*

vivo or *in vitro*, or reduced *in vivo* side-effects as compared to the underivatized antibody.

        Other derivatives of anti- IGF-1R antibodies within the scope of this invention include covalent or

aggregative conjugates of anti-IGF-1R antibodies, or fragments thereof, with other proteins or polypeptides,

25   such as by expression of recombinant fusion proteins comprising heterologous polypeptides fused to the N-

terminus or C-terminus of an anti- IGF-1R antibody polypeptide. For example, the conjugated peptide may

be a heterologous signal (or leader) polypeptide, e.g., the yeast alpha-factor leader, or a peptide such as an

epitope tag. Antigen binding protein-containing fusion proteins can comprise peptides added to facilitate

purification or identification of antigen binding protein (e.g., poly-His). An antigen binding protein also

30   can be linked to the FLAG peptide Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys (DYKDDDDK) (SEQ ID NO:255)

as described in Hopp et al., *Bio/Technology* 6:1204, 1988, and U.S. Patent 5,011,912. The FLAG peptide is

highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody (mAb),

enabling rapid assay and facile purification of expressed recombinant protein. Reagents useful for

preparing fusion proteins in which the FLAG peptide is fused to a given polypeptide are commercially

35   available (Sigma, St. Louis, MO).

        Oligomers that contain one or more antigen binding proteins may be employed as IGF-1R

antagonists. Oligomers may be in the form of covalently-linked or non-covalently-linked dimers, trimers,

or higher oligomers. Oligomers comprising two or more antigen binding protein are contemplated for use,

with one example being a homodimer. Other oligomers include heterodimers, homotrimers, heterotrimers,

40   homotetramers, heterotetramers, *etc.*

One embodiment is directed to oligomers comprising multiple antigen binding proteins joined *via* covalent or non-covalent interactions between peptide moieties fused to the antigen binding proteins. Such peptides may be peptide linkers (spacers), or peptides that have the property of promoting oligomerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote

5   oligomerization of antigen binding proteins attached thereto, as described in more detail below.

In particular embodiments, the oligomers comprise from two to four antigen binding proteins. The antigen binding proteins of the oligomer may be in any form, such as any of the forms described above, *e.g.*, variants or fragments. Preferably, the oligomers comprise antigen binding proteins that have IGF-1R binding activity.

10   In one embodiment, an oligomer is prepared using polypeptides derived from immunoglobulins. Preparation of fusion proteins comprising certain heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described, *e.g.*, by Ashkenazi *et al.*, 1991, PNAS USA 88:10535; Byrn *et al.*, 1990, Nature 344:677; and Hollenbaugh *et al.*, 1992 "Construction of Immunoglobulin Fusion Proteins", in *Current Protocols in Immunology*, Suppl. 4, pages 10.19.1 -

15   10.19.11.

One embodiment of the present invention is directed to a dimer comprising two fusion proteins created by fusing an IGF-1R binding fragment of an anti- IGF-1R antibody to the Fc region of an antibody. The dimer can be made by, for example, inserting a gene fusion encoding the fusion protein into an appropriate expression vector, expressing the gene fusion in host cells transformed with the recombinant

20   expression vector, and allowing the expressed fusion protein to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc moieties to yield the dimer.

The term "Fc polypeptide" as used herein includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising Fc moieties (and

25   oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

One suitable Fc polypeptide, described in PCT application WO 93/10151 (hereby incorporated by reference), is a single chain polypeptide extending from the N-terminal hinge region to the native C-terminus of the Fc region of a human IgG1 antibody. Another useful Fc polypeptide is the Fc mutein

30   described in U.S. Patent 5,457,035 and in Baum *et al.*, 1994, EMBO J. 13:3992-4001. The amino acid sequence of this mutein is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. The mutein exhibits reduced affinity for Fc receptors.

In other embodiments, the variable portion of the heavy and/or light chains of an anti- IGF-1R

35   antibody may be substituted for the variable portion of an antibody heavy and/or light chain.

Alternatively, the oligomer is a fusion protein comprising multiple antigen binding proteins, with or without peptide linkers (spacer peptides). Among the suitable peptide linkers are those described in U.S. Patents 4,751,180 and 4,935,233.

Another method for preparing oligomeric antigen binding proteins involves use of a leucine zipper.

40   Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found.

Leucine zippers were originally identified in several DNA-binding proteins (Landschulz *et al.*, 1988, Science 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in PCT application

5   WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe *et al.*, 1994, FEBS Letters 344:191, hereby incorporated by reference. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow *et al.*, 1994, Semin. Immunol. 6:267-78. In one approach, recombinant fusion proteins comprising an anti- IGF-1R antibody fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and

10   the soluble oligomeric anti- IGF-1R antibody fragments or derivatives that form are recovered from the culture supernatant.

In one aspect, the present invention provides antigen binding proteins that interfere with the binding of IGF-1 and/or IGF-2 to an IGF-1R. Such antigen binding proteins can be made against IGF-1R, or a fragment, variant or derivative thereof, and screened in conventional assays for the ability to interfere

15   with binding of IGF-1 and/or IGF-2 to IGF-1R. Examples of suitable assays are assays that test the antigen binding proteins for the ability to inhibit binding of IGF-1 and/or IGF-2 to cells expressing IGF-1R, or that test antigen binding proteins for the ability to reduce a biological or cellular response that results from the binding of IGF-1 and/or IGF-2 to cell surface IGF-1R receptors.

In another aspect, the present invention provides an antigen binding protein that blocks the binding

20   of IGF-1 and/or IGF-2 to IGF-1R but does not significantly block the binding of insulin to insulin receptor (INS-R). In one embodiment, the antigen binding protein does not bind to INS-R. In another embodiment, the antigen binding protein binds to the INS-R with such a low affinity that it does not effectively block the binding of insulin to INS-R. In another embodiment, the antigen binding protein binds to INS-R, but antigen binding protein-bound INS-R can still bind to insulin. In another embodiment, the antigen binding

25   protein's selectivity for IGF-1R is at least 50 times greater than its selectivity for insulin receptor. In another embodiment, the selectivity of the antigen binding protein is more than 100 times greater than its selectivity for insulin receptor.

In another aspect, the present invention provides an antigen binding protein that demonstrates species selectivity. In one embodiment, the antigen binding protein binds to one or more mammalian IGF-

30   1R, for example, to human IGF-1R and one or more of mouse, rat, guinea pig, hamster, gerbil, cat, rabbit, dog, goat, sheep, cow, horse, camel, and non-human primate IGF-1R. In another embodiment, the antigen binding protein binds to one or more primate IGF-1R, for example, to human IGF-1R and one or more of cynomologous, marmoset, rhesus, and chimpanzee IGF-1R. In another embodiment, the antigen binding protein binds specifically to human, cynomologous, marmoset, rhesus, or chimpanzee IGF-1R. In another

35   embodiment, the antigen binding protein does not bind to one or more of mouse, rat, guinea pig, hamster, gerbil, cat, rabbit, dog, goat, sheep, cow, horse, camel, and non-human primate IGF-1R. In another embodiment, the antigen binding protein does not bind to a New World monkey species such as a marmoset. In another embodiment, the antigen binding protein does not exhibit specific binding to any naturally occurring protein other than IGF-1R. In another embodiment, the antigen binding protein does

40   not exhibit specific binding to any naturally occurring protein other than mammalian IGF-1R. In another

embodiment, the antigen binding protein does not exhibit specific binding to any naturally occurring protein other than primate IGF-1R. In another embodiment, the antigen binding protein does not exhibit specific binding to any naturally occurring protein other than human IGF-1R. In another embodiment, the antigen binding protein specifically binds to mouse, rat, cynomolgus monkey, and human IGF-1R. In another

5   embodiment, the antigen binding protein specifically binds to mouse, rat, cynomolgus monkey, and human IGF-1R with a similar binding affinity. In another embodiment, the antigen binding protein blocks binding of human IGF-1 and IGF-2 with mouse, rat, cynomolgus monkey, and human IGF-1R. In another embodiment, the antigen binding protein blocks binding of human IGF-1 and IGF-2 with mouse, rat, cynomolgus monkey, and human IGF-1R with similar K_i. In another embodiment, the antigen binding

10 protein blocks binding of human IGF-1 and IGF-2 with mouse, rat, cynomolgus monkey, and human IGF-1R with a K_i of between about 0.57 and about 0.61 nM.

One may determine the selectivity of an antigen binding protein for an IGF-1R using methods well known in the art and following the teachings of the specification. For example, one may determine the selectivity using Western blot, FACS, ELISA or RIA.

15 In another aspect, the present invention provides an IGF-1R binding antigen binding protein (for example, an anti-IGF-1R antibody), that has one or more of the following characteristics: binds to both human and murine IGF-1R, inhibits the binding of both IGF-1 and IGF-2 to human IGF-1R, inhibits the binding of both IGF-1 and IGF-2 to murine IGF-1R, preferentially inhibits the high affinity binding of IGF-1 and/or of IGF-2 to IGF-1R, binds to the L2 domain of IGF-1R, causes relatively little down-regulation of

20 cell-surface expressed IGF-1R after 17 hours of exposure (as compared to MAB391 (R&D systems, Minneapolis, MN); e.g., amount of IGF-1R is reduced by less than 20%), causes a level of down-regulation of cell-surface expressed IGF-1R on Colo-205 or MiaPaCa-2 xenograft tumor cells in mice as MAB391 after four weeks of once weekly doses of 200 micrograms.

Antigen-binding fragments of antigen binding proteins of the invention may be produced by

25 conventional techniques. Examples of such fragments include, but are not limited to, Fab and $F(ab')_2$ fragments. Antibody fragments and derivatives produced by genetic engineering techniques also are contemplated.

Additional embodiments include chimeric antibodies, e.g., humanized versions of non-human (e.g., murine) monoclonal antibodies. Such humanized antibodies may be prepared by known techniques,

30 and offer the advantage of reduced immunogenicity when the antibodies are administered to humans. In one embodiment, a humanized monoclonal antibody comprises the variable domain of a murine antibody (or all or part of the antigen binding site thereof) and a constant domain derived from a human antibody. Alternatively, a humanized antibody fragment may comprise the antigen binding site of a murine monoclonal antibody and a variable domain fragment (lacking the antigen-binding site) derived from a

35 human antibody. Procedures for the production of chimeric and further engineered monoclonal antibodies include those described in Riechmann et al., 1988, Nature 332:323, Liu et al., 1987, Proc. Nat. Acad. Sci. USA 84:3439, Larrick et al., 1989, Bio/Technology 7:934, and Winter et al., 1993, TIPS 14:139. In one embodiment, the chimeric antibody is a CDR grafted antibody. Techniques for humanizing antibodies are discussed in, e.g., U.S. Pat. App. No. 10/194,975 (published February 27, 2003), U.S. Pat. No.s 5,869,619,

5,225,539, 5,821,337, 5,859,205, Padlan *et al.*, 1995, FASEB J. 9:133-39, and Tamura *et al.*, 2000, J. Immunol. 164:1432-41.

Procedures have been developed for generating human or partially human antibodies in non-human animals. For example, mice in which one or more endogenous immunoglobulin genes have been

5   inactivated by various means have been prepared. Human immunoglobulin genes have been introduced into the mice to replace the inactivated mouse genes. Antibodies produced in the animal incorporate human immunoglobulin polypeptide chains encoded by the human genetic material introduced into the animal. In one embodiment, a non-human animal, such as a transgenic mouse, is immunized with an IGF-1R polypeptide, such that antibodies directed against the IGF-1R polypeptide are generated in the animal. One

10   example of a suitable immunogen is a soluble human IGF-1R, such as a polypeptide comprising the extracellular domain of the protein of Figure 10, or other immunogenic fragment of the protein of Figure 10. Examples of techniques for production and use of transgenic animals for the production of human or partially human antibodies are described in U.S. Patents 5,814,318, 5,569,825, and 5,545,806, Davis *et al.*, 2003, *Production of human antibodies from transgenic mice* in Lo, ed. Antibody Engineering: Methods and

15   Protocols, Humana Press, NJ:191-200, Kellermann *et al.*, 2002, Curr Opin Biotechnol. 13:593-97, Russel *et al.*, 2000, Infect Immun. 68:1820-26, Gallo *et al.*, 2000, Eur J Immun. 30:534-40, Davis *et al.*, 1999, Cancer Metastasis Rev. 18:421-25, Green, 1999, J Immunol Methods. 231:11-23, Jakobovits, 1998, Advanced Drug Delivery Reviews 31:33-42, Green *et al.*, 1998, J Exp Med. 188:483-95, Jakobovits A, 1998, Exp. Opin. Invest. Drugs. 7:607-14, Tsuda *et al.*, 1997, Genomics. 42:413-21, Mendez *et al.*, 1997, Nat Genet.

20   15:146-56, Jakobovits, 1994, Curr Biol. 4:761-63, Arbones *et al.*, 1994, Immunity. 1:247-60, Green *et al.*, 1994, Nat Genet. 7:13-21, Jakobovits *et al.*, 1993, Nature. 362:255-58, Jakobovits *et al.*, 1993, Proc Natl Acad Sci U S A. 90:2551-55. Chen, J., M. Trounstine, F. W. Alt, F. Young, C. Kurahara, J. Loring, D. Huszar. "Immunoglobulin gene rearrangement in B cell deficient mice generated by targeted deletion of the JH locus." International Immunology 5 (1993): 647-656, Choi *et al.*, 1993, Nature Genetics 4: 117-23,

25   Fishwild *et al.*, 1996, Nature Biotechnology 14: 845-51, Harding *et al.*, 1995, Annals of the New York Academy of Sciences, Lonberg *et al.*, 1994, Nature 368: 856-59, Lonberg, 1994, *Transgenic Approaches to Human Monoclonal Antibodies* in Handbook of Experimental Pharmacology 113: 49-101, Lonberg *et al.*, 1995, Internal Review of Immunology 13: 65-93, Neuberger, 1996, Nature Biotechnology 14: 826, Taylor *et al.*, 1992, Nucleic Acids Research 20: 6287-95, Taylor *et al.*, 1994, International Immunology 6: 579-91,

30   Tomizuka *et al.*, 1997, Nature Genetics 16: 133-43, Tomizuka *et al.*, 2000, Proceedings of the National Academy of Sciences USA 97: 722-27, Tuaillon *et al.*, 1993, Proceedings of the National Academy of Sciences USA 90: 3720-24, and Tuaillon *et al.*, 1994, Journal of Immunology 152: 2912-20.

In another aspect, the present invention provides monoclonal antibodies that bind to IGF-1R. Monoclonal antibodies may be produced using any technique known in the art, *e.g.*, by immortalizing

35   spleen cells harvested from the transgenic animal after completion of the immunization schedule. The spleen cells can be immortalized using any technique known in the art, *e.g.*, by fusing them with myeloma cells to produce hybridomas. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells

40   (hybridomas). Examples of suitable cell lines for use in mouse fusions include Sp-20, P3-X63/Ag8, P3-

X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XX0 Bul; examples of cell lines used in rat fusions include R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

5   In one embodiment, a hybridoma cell line is produced by immunizing an animal (*e.g.*, a transgenic animal having human immunoglobulin sequences) with an IGF-1R immunogen; harvesting spleen cells from the immunized animal; fusing the harvested spleen cells to a myeloma cell line, thereby generating hybridoma cells; establishing hybridoma cell lines from the hybridoma cells, and identifying a hybridoma cell line that produces an antibody that binds an IGF-1R polypeptide. Such hybridoma cell lines, and anti-IGF-1R monoclonal antibodies produced by them, are encompassed by the present invention.

10   Monoclonal antibodies secreted by a hybridoma cell line can be purified using any technique known in the art. Hybridomas or mAbs may be further screened to identify mAbs with particular properties, such as the ability to block an IGF-1 and/or IGF-2 induced activity. Examples of such screens are provided in the examples below.

        Molecular evolution of the complementarity determining regions (CDRs) in the center of the
15   antibody binding site also has been used to isolate antibodies with increased affinity, for example, antibodies having increased affinity for c-erbB-2, as described by Schier *et al.*, 1996, J. Mol. Biol. 263:551. Accordingly, such techniques are useful in preparing antibodies to IGF-1R.

        Antigen binding proteins directed against an IGF-1R can be used, for example, in assays to detect the presence of IGF-1R polypeptides, either *in vitro* or *in vivo*. The antigen binding proteins also may be
20   employed in purifying IGF-1R proteins by immunoaffinity chromatography. Those antigen binding proteins that additionally can block binding of IGF-1 and/or IGF-2 to IGF-1R may be used to inhibit a biological activity that results from such binding. Blocking antigen binding proteins can be used in the methods of the present invention. Such antigen binding proteins that function as IGF-1 and/or IGF-2 antagonists may be employed in treating any IGF-1 and/or IGF-2-induced condition, including but not
25   limited to cancer. In one embodiment, a human anti- IGF-1R monoclonal antibody generated by procedures involving immunization of transgenic mice is employed in treating such conditions.

        Antigen binding proteins may be employed in an *in vitro* procedure, or administered *in vivo* to inhibit an IGF-1 and/or IGF-2-induced biological activity. Disorders caused or exacerbated (directly or indirectly) by the interaction of IGF-1 and/or IGF-2 with cell surface IGF-1R, examples of which are
30   provided above, thus may be treated. In one embodiment, the present invention provides a therapeutic method comprising *in vivo* administration of an IGF-1 and/or IGF-2 blocking antigen binding protein to a mammal in need thereof in an amount effective for reducing an IGF-1 and/or IGF-2-induced biological activity.

        Antigen binding proteins of the invention include partially human and fully human monoclonal
35   antibodies that inhibit a biological activity of IGF-1 and also inhibit a biological activity of IGF-2. One embodiment is directed to a human monoclonal antibody that at least partially blocks binding of IGF-1 and of IGF-2 to a cell that expresses human IGF-1R. In one embodiment, the antibodies are generated by immunizing a transgenic mouse with an IGF-1R immunogen. In another embodiment, the immunogen is a human IGF-1R polypeptide (e.g., a soluble fragment comprising all or part of the IGF-1R extracellular

domain). Hybridoma cell lines derived from such immunized mice, wherein the hybridoma secretes a
monoclonal antibody that binds IGF-1R, also are provided herein.

5   Although human, partially human, or humanized antibodies will be suitable for many applications,
particularly those involving administration of the antibody to a human subject, other types of antigen
binding proteins will be suitable for certain applications. The non-human antibodies of the invention can
be, for example, derived from any antibody-producing animal, such as mouse, rat, rabbit, goat, donkey, or
non-human primate (such as monkey (*e.g.*, cynomologous or rhesus monkey) or ape (*e.g.*, chimpanzee)).
Non-human antibodies of the invention can be used, for example, in *in vitro* and cell-culture based
applications, or any other application where an immune response to the antibody of the invention does not
10 occur, is insignificant, can be prevented, is not a concern, or is desired. In one embodiment, a non-human
antibody of the invention is administered to a non-human subject. In another embodiment, the non-human
antibody does not elicit an immune response in the non-human subject. In another embodiment, the non-
human antibody is from the same species as the non-human subject, *e.g.*, a mouse antibody of the invention
is administered to a mouse. An antibody from a particular species can be made by, for example,
15 immunizing an animal of that species with the desired immunogen (*e.g.*, a soluble IGF-1R polypeptide) or
using an artificial system for generating antibodies of that species (*e.g.*, a bacterial or phage display-based
system for generating antibodies of a particular species), or by converting an antibody from one species into
an antibody from another species by replacing, *e.g.*, the constant region of the antibody with a constant
region from the other species, or by replacing one or more amino acid residues of the antibody so that it
20 more closely resembles the sequence of an antibody from the other species. In one embodiment, the
antibody is a chimeric antibody comprising amino acid sequences derived from antibodies from two or
more different species.

        Antigen binding proteins may be prepared by any of a number of conventional techniques. For
example, they may be purified from cells that naturally express them (e.g., an antibody can be purified from
25 a hybridoma that produces it), or produced in recombinant expression systems, using any technique known
in the art. See, for example, *Monoclonal Antibodies, Hybridomas: A New Dimension in Biological
Analyses*, Kennet *et al.* (eds.), Plenum Press, New York (1980); and *Antibodies: A Laboratory Manual*,
Harlow and Land (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1988).

        Any expression system known in the art can be used to make the recombinant polypeptides of the
30 invention. In general, host cells are transformed with a recombinant expression vector that comprises DNA
encoding a desired polypeptide. Among the host cells that may be employed are prokaryotes, yeast or
higher eukaryotic cells. Prokaryotes include gram negative or gram positive organisms, for example *E. coli*
or bacilli. Higher eukaryotic cells include insect cells and established cell lines of mammalian origin.
Examples of suitable mammalian host cell lines include the COS-7 line of monkey kidney cells (ATCC
35 CRL 1651) (Gluzman *et al.*, 1981, Cell 23:175), L cells, 293 cells, C127 cells, 3T3 cells (ATCC CCL 163),
Chinese hamster ovary (CHO) cells, HeLa cells, BHK (ATCC CRL 10) cell lines, and the CVI/EBNA cell
line derived from the African green monkey kidney cell line CVI (ATCC CCL 70) as described by
McMahan *et al.*, 1991, EMBO J. 10: 2821. Appropriate cloning and expression vectors for use with
bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels *et al.* (*Cloning Vectors: A
40 Laboratory Manual*, Elsevier, New York, 1985).

The transformed cells can be cultured under conditions that promote expression of the polypeptide, and the polypeptide recovered by conventional protein purification procedures. One such purification procedure includes the use of affinity chromatography, *e.g.*, over a matrix having all or a portion (*e.g.*, the extracellular domain) of IGF-1R bound thereto. Polypeptides contemplated for use herein include

5   substantially homogeneous recombinant mammalian anti- IGF-1R antibody polypeptides substantially free of contaminating endogenous materials.

Antigen binding proteins may be prepared, and screened for desired properties, by any of a number of known techniques. Certain of the techniques involve isolating a nucleic acid encoding a polypeptide chain (or portion thereof) of an antigen binding protein of interest (e.g., an anti-IGF-1R antibody), and

10   manipulating the nucleic acid through recombinant DNA technology. The nucleic acid may be fused to another nucleic acid of interest, or altered (*e.g.*, by mutagenesis or other conventional techniques) to add, delete, or substitute one or more amino acid residues, for example.

In one aspect, the present invention provides antigen-binding fragments of an anti-IGF-1R antibody of the invention. Such fragments can consist entirely of antibody-derived sequences or can

15   comprise additional sequences. Examples of antigen-binding fragments include Fab, F(ab')2, single chain antibodies, diabodies, triabodies, tetrabodies, and domain antibodies. Other examples are provided in Lunde *et al.*, 2002, Biochem. Soc. Trans. 30:500-06.

Single chain antibodies may be formed by linking heavy and light chain variable domain (Fv region) fragments via an amino acid bridge (short peptide linker), resulting in a single polypeptide chain.

20   Such single-chain Fvs (scFvs) have been prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable domain polypeptides (V_L and V_H). The resulting polypeptides can fold back on themselves to form antigen-binding monomers, or they can form multimers (*e.g.*, dimers, trimers, or tetramers), depending on the length of a flexible linker between the two variable domains (Kortt *et al.*, 1997, Prot. Eng. 10:423; Kortt *et al.*, 2001, Biomol. Eng. 18:95-108). By combining different V_L and V_H-

25   comprising polypeptides, one can form multimeric scFvs that bind to different epitopes (Kriangkum *et al.*, 2001, Biomol. Eng. 18:31-40). Techniques developed for the production of single chain antibodies include those described in U.S. Patent No. 4,946,778; Bird, 1988, Science 242:423; Huston *et al.*, 1988, Proc. Natl. Acad. Sci. USA 85:5879; Ward *et al.*, 1989, Nature 334:544, de Graaf *et al.*, 2002, Methods Mol Biol. 178:379-87. Single chain antibodies derived from antibodies provided herein include, but are not limited

30   to, scFvs comprising the variable domain combinations L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51,

35   and L52H52) are encompassed by the present invention.

Antigen binding proteins (e.g., antibodies, antibody fragments, and antibody derivatives) of the invention can comprise any constant region known in the art. The light chain constant region can be, for example, a kappa- or lambda-type light chain constant region, *e.g.*, a human kappa- or lambda-type light chain constant region. The heavy chain constant region can be, for example, an alpha-, delta-, epsilon-,

40   gamma-, or mu-type heavy chain constant regions, *e.g.*, a human alpha-, delta-, epsilon-, gamma-, or mu-

type heavy chain constant region. In one embodiment, the light or heavy chain constant region is a fragment, derivative, variant, or mutein of a naturally occurring constant region.

Techniques are known for deriving an antibody of a different subclass or isotype from an antibody of interest, *i.e.*, subclass switching. Thus, IgG antibodies may be derived from an IgM antibody, for
5 example, and *vice versa*. Such techniques allow the preparation of new antibodies that possess the antigen-binding properties of a given antibody (the parent antibody), but also exhibit biological properties associated with an antibody isotype or subclass different from that of the parent antibody. Recombinant DNA techniques may be employed. Cloned DNA encoding particular antibody polypeptides may be employed in such procedures, *e.g.*, DNA encoding the constant domain of an antibody of the desired
10 isotype. See also Lantto *et al.*, 2002, Methods Mol. Biol.178:303-16.

In one embodiment, an antigen binding protein of the invention comprises the IgG1 heavy chain domain of Figure 13 or a fragment of the IgG1 heavy chain domain of Figure 13. In another embodiment, an antigen binding protein of the invention comprises the kappa light chain constant chain region of Figure 13 or a fragment of the kappa light chain constant region of Figure 13. In another embodiment, an antigen
15 binding protein of the invention comprises both the IgG1 heavy chain domain, or a fragment thereof, of Figure 13 and the kappa light chain domain, or a fragment thereof, of Figure 13.

Accordingly, the antigen binding proteins of the present invention include those comprising, for example, the variable domain combinations L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20,
20 L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52, having a desired isotype (for example, IgA, IgG1, IgG2, IgG3, IgG4, IgM, IgE, and IgD) as well as Fab or F(ab')$_2$ fragments thereof. Moreover, if an IgG4 is desired, it may also be desired to introduce a point mutation
25 (CPSCP -> CPPCP) in the hinge region as described in Bloom *et al.*, 1997, Protein Science 6:407, incorporated by reference herein) to alleviate a tendency to form intra-H chain disulfide bonds that can lead to heterogeneity in the IgG4 antibodies.

Moreover, techniques for deriving antigen binding proteins having different properties (*i.e.*, varying affinities for the antigen to which they bind) are also known. One such technique, referred to as
30 chain shuffling, involves displaying immunoglobulin variable domain gene repertoires on the surface of filamentous bacteriophage, often referred to as phage display. Chain shuffling has been used to prepare high affinity antibodies to the hapten 2-phenyloxazol-5-one, as described by Marks *et al.*, 1992, BioTechnology, 10:779.

In particular embodiments, antigen binding proteins of the present invention have a binding
35 affinity (K_a) for IGF-1R of at least 10^6, measured as described in the Examples. In other embodiments, the antigen binding proteins exhibit a K_a of at least 10^7, at least 10^8, at least 10^9, or at least 10^{10}.

In another embodiment, the present invention provides an antigen binding protein that has a low dissociation rate from IGF-1R. In one embodiment, the antigen binding protein has a K_{off} of 1×10^{-4} s^{-1} or lower. In another embodiment, the K_{off} is 5×10^{-5} s^{-1} or lower. In another embodiment, the K_{off} is
40 substantially the same as an antibody having a combination of light chain and heavy chain variable domain

sequences selected from the group of combinations consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40,

5   L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52. In another embodiment, the antigen binding protein binds to IGF-1R with substantially the same K_{off} as an antibody that comprises one or more CDRs from an antibody having a combination of light chain and heavy chain variable domain sequences selected from the group of combinations consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13,

10   L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52. In another embodiment, the antigen binding protein binds to IGF-1R with substantially the same K_{off} as an antibody that comprises one of the amino

15   acid sequences illustrated in Figures 2 through 9. In another embodiment, the antigen binding protein binds to IGF-1R with substantially the same K_{off} as an antibody that comprises one or more CDRs from an antibody that comprises one of the amino acid sequences illustrated in Figures 2 through 9.

In another aspect, the present invention provides an antigen binding protein that binds to the L2 domain of human IGF-1R. Antigen binding proteins that bind to the L2 domain can be made using any

20   technique known in the art. For example, such antigen binding proteins can be isolated using the full-length IGF-1R polypeptide (e.g., in a membrane-bound preparation), a soluble extracellular domain fragment of IGF-1R (an example of which is provided in Example 1), or a smaller fragment of the IGF-1R extracellular domain comprising or consisting of the L2 domain (examples of which are provided in Example 10). Antigen binding proteins so isolated can be screened to determine their binding specificity using any

25   method known in the art (an example of which is provided in Example 10).

In another aspect, the present invention provides an antigen binding protein that binds to human IGF-1R expressed on the surface of a cell and, when so bound, inhibits IGF-1R signaling activity in the cell without causing a significant reduction in the amount of IGF-1R on the surface of the cell. Any method for determining or estimating the amount of IGF-1R on the surface and/or in the interior of the cell can be used.

30   In one embodiment, the present invention provides an antigen binding protein that binds to the L2 domain of a human IGF-1R expressed on the surface of a cell and, when so bound, inhibits IGF-1R signaling activity in the cell without significantly increasing the rate of internalization of the IGF-1R from the surface of the cell. In other embodiments, binding of the antigen binding protein to the IGF-1R-expressing cell causes less than about 75%, 50%, 40%, 30%, 20%, 15%, 10%, 5%, 1%, or 0.1% of the cell-surface IGF-1R

35   to be internalized. In another aspect, binding of the antigen binding protein to the IGF-1R-expressing cell causes a gradual reduction in the amount of IGF-1R on the cell surface such that within a few hours of contacting the cell with the antigen binding protein, little or no decrease in cell surface IGF-1R is detected, but, after several days or weeks of exposure of the cell to the antigen binding protein, a marked decrease in cell surface IGF-1R is detected.

In another aspect, the present invention provides an antigen binding protein having a half-life of at least one day *in vitro* or *in vivo* (*e.g.*, when administered to a human subject). In one embodiment, the antigen binding protein has a half-life of at least three days. In another embodiment, the antigen binding protein has a half-life of four days or longer. In another embodiment, the antigen binding protein has a

5   half-life of eight days or longer. In another embodiment, the antigen binding protein is derivatized or modified such that it has a longer half-life as compared to the underivatized or unmodified antigen binding protein. In another embodiment, the antigen binding protein contains one or more point mutations to increase serum half life, such as described in WO 00/09560, published Feb.24, 2000, incorporated by reference.

10   The present invention further provides multi-specific antigen binding proteins, for example, bispecific antigen binding protein, *e.g.*, antigen binding protein that bind to two different epitopes of IGF-1R, or to an epitope of IGF-1R and an epitope of another molecule, via two different antigen binding sites or regions. Moreover, bispecific antigen binding protein as disclosed herein can comprise an IGF-1R binding site from one of the herein-described antibodies and a second IGF-1R binding region from another

15   of the herein-described antibodies, including those described herein by reference to other publications. Alternatively, a bispecific antigen binding protein may comprise an antigen binding site from one of the herein described antibodies and a second antigen binding site from another IGF-1R antibody that is known in the art, or from an antibody that is prepared by known methods or the methods described herein.

Numerous methods of preparing bispecific antibodies are known in the art, and discussed in US

20   Patent Application 09/839,632, filed April 20, 2001 (incorporated by reference herein). Such methods include the use of hybrid-hybridomas as described by Milstein *et al.*, 1983, Nature 305:537, and others (U.S. Patent 4,474,893, U.S. Patent 6,106,833), and chemical coupling of antibody fragments (Brennan *et al.*,1985, Science 229:81; Glennie *et al.*,1987, J. Immunol. 139:2367; U.S. Patent 6,010,902). Moreover, bispecific antibodies can be produced via recombinant means, for example by using leucine zipper moieties

25   (*i.e.*, from the Fos and Jun proteins, which preferentially form heterodimers; Kostelny *et al.*, 1992, J. Immmol. 148:1547) or other lock and key interactive domain structures as described in U.S. Patent 5,582,996. Additional useful techniques include those described in Kortt *et al.*, 1997, *supra*; U.S. Patent 5,959,083; and U.S. Patent 5,807,706.

In another aspect, the antigen binding protein of the present invention comprises a derivative of an

30   antibody. The derivatized antibody can comprise any molecule or substance that imparts a desired property to the antibody, such as increased half-life in a particular use. The derivatized antibody can comprise, for example, a detectable (or labeling) moiety (*e.g.*, a radioactive, colorimetric, antigenic or enzymatic molecule, a detecable bead (such as a magnetic or electrodense (*e.g.*, gold) bead), or a molecule that binds to another molecule (*e.g.*, biotin or streptavidin)), a therapeutic or diagnostic moiety (*e.g.*, a radioactive,

35   cytotoxic, or pharmaceutically active moiety), or a molecule that increases the suitability of the antibody for a particular use (*e.g.*, administration to a subject, such as a human subject, or other *in vivo* or *in vitro* uses). Examples of molecules that can be used to derivatize an antibody include albumin (*e.g.*, human serum albumin) and polyethylene glycol (PEG). Albumin-linked and PEGylated derivatives of antibodies can be prepared using techniques well known in the art. In one embodiment, the antibody is conjugated or

40   otherwise linked to transthyretin (TTR) or a TTR variant. The TTR or TTR variant can be chemically

modified with, for example, a chemical selected from the group consisting of dextran, poly(n-vinyl pyurrolidone), polyethylene glycols, propropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohols. US Pat. App. No. 20030195154.

5   In another aspect, the present invention provides methods of screening for a molecule that binds to IGF-1R using the antigen binding proteins of the present invention. Any suitable screening technique can be used. In one embodiment, an IGF-1R molecule, or a fragment thereof to which an antigen binding protein of the present invention binds, is contacted with the antigen binding protein of the invention and with another molecule, wherein the other molecule binds to IGF-1R if it reduces the binding of the antigen binding protein to IGF-1R. Binding of the antigen binding protein can be detected using any suitable

10   method, e.g., an ELISA. Detection of binding of the antigen binding protein to IGF-1R can be simplified by detectably labeling the antigen binding protein, as discussed above. In another embodiment, the IGF-1R-binding molecule is further analyzed to determine whether it inhibits IGF-1R, IGF-1, and/or IGF-2-mediated signaling.

15   Nucleic acids

In one aspect, the present invention provides isolated nucleic acid molecules. The nucleic acids comprise, for example, polynucleotides that encode all or part of an antigen binding protein , for example, one or both chains of an antibody of the invention, or a fragment, derivative, mutein, or variant thereof, polynucleotides sufficient for use as hybridization probes, PCR primers or sequencing primers for

20   identifying, analyzing, mutating or amplifying a polynucleotide encoding a polypeptide, anti-sense nucleic acids for inhibiting expression of a polynucleotide, and complementary sequences of the foregoing. The nucleic acids can be any length. They can be, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 750, 1,000, 1,500, 3,000, 5,000 or more nucleotides in length, and/or can comprise one or more additional sequences, for example, regulatory sequences, and/or be

25   part of a larger nucleic acid, for example, a vector. The nucleic acids can be single-stranded or double-stranded and can comprise RNA and/or DNA nucleotides, and artificial variants thereof (e.g., peptide nucleic acids).

Nucleic acids encoding antibody polypeptides (e.g., heavy or light chain, variable domain only, or full length) may be isolated from B-cells of mice that have been immunized with IGF-1R. The nucleic acid

30   may be isolated by conventional procedures such as polymerase chain reaction (PCR).

Figure 1 provides nucleic acid sequences encoding the variable regions of the heavy and light chain variable regions shown in Figures 2 and 3. The skilled artisan will appreciate that, due to the degeneracy of the genetic code, each of the polypeptide sequences in Figures 2 through 9 also is encoded by a large number of other nucleic acid sequences. The present invention provides each degenerate nucleotide

35   sequence encoding each antigen binding protein of the invention.

The invention further provides nucleic acids that hybridize to other nucleic acids (e.g., nucleic acids comprising a nucleotide sequence of Figure 1) under particular hybridization conditions. Methods for hybridizing nucleic acids are well-known in the art. See, e.g., Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. As defined herein, a moderately stringent hybridization condition

40   uses a prewashing solution containing 5X sodium chloride/sodium citrate (SSC), 0.5% SDS, 1.0 mM EDTA

(pH 8.0), hybridization buffer of about 50% formamide, 6X SSC, and a hybridization temperature of 55° C (or other similar hybridization solutions, such as one containing about 50% formamide, with a hybridization temperature of 42° C), and washing conditions of 60° C, in 0.5X SSC, 0.1% SDS. A stringent hybridization condition hybridizes in 6X SSC at 45° C, followed by one or more washes in 0.1X SSC, 0.2%

5   SDS at 68° C. Furthermore, one of skill in the art can manipulate the hybridization and/or washing conditions to increase or decrease the stringency of hybridization such that nucleic acids comprising nucleotide sequences that are at least 65, 70, 75, 80, 85, 90, 95, 98 or 99% identical to each other typically remain hybridized to each other. The basic parameters affecting the choice of hybridization conditions and guidance for devising suitable conditions are set forth by, for example, Sambrook, Fritsch, and Maniatis

10   (1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 9 and 11; and Current Protocols in Molecular Biology, 1995, Ausubel *et al.*, eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4), and can be readily determined by those having ordinary skill in the art based on, for example, the length and/or base composition of the DNA.

Changes can be introduced by mutation into a nucleic acid, thereby leading to changes in the

15   amino acid sequence of a polypeptide (*e.g.*, an antigen binding protein) that it encodes. Mutations can be introduced using any technique known in the art. In one embodiment, one or more particular amino acid residues are changed using, for example, a site-directed mutagenesis protocol. In another embodiment, one or more randomly selected residues is changed using, for example, a random mutagenesis protocol. However it is made, a mutant polypeptide can be expressed and screened for a desired property (*e.g.*,

20   binding to IGF-1R or blocking the binding of IGF-1 and/or IGF-2 to IGF-1R).

Mutations can be introduced into a nucleic acid without significantly altering the biological activity of a polypeptide that it encodes. For example, one can make nucleotide substitutions leading to amino acid substitutions at non-essential amino acid residues. In one embodiment, a nucleotide sequence provided in Figure 1, or a desired fragment, variant, or derivative thereof, is mutated such that it encodes an

25   amino acid sequence comprising one or more deletions or substitutions of amino acid residues that are shown in Figures 2 through 9 to be residues where two or more sequences differ. In another embodiment, the mutagenesis inserts an amino acid adjacent to one or more amino acid residues shown in Figures 2 through 9 to be residues where two or more sequences differ. Alternatively, one or more mutations can be introduced into a nucleic acid that selectively change the biological activity (*e.g.*, binding of IGF-1R,

30   inhibiting IGF-1 and/or IGF-2, *etc.*) of a polypeptide that it encodes. For example, the mutation can quantitatively or qualitatively change the biological activity. Examples of quantitative changes include increasing, reducing or eliminating the activity. Examples of qualitative changes include changing the antigen specificity of an antigen binding protein.

In another aspect, the present invention provides nucleic acid molecules that are suitable for use as

35   primers or hybridization probes for the detection of nucleic acid sequences of the invention. A nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence encoding a full-length polypeptide of the invention, for example, a fragment that can be used as a probe or primer or a fragment encoding an active portion (*e.g.*, an IGF-1R binding portion) of a polypeptide of the invention.

Probes based on the sequence of a nucleic acid of the invention can be used to detect the nucleic

40   acid or similar nucleic acids, for example, transcripts encoding a polypeptide of the invention. The probe

can comprise a label group, *e.g.*, a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used to identify a cell that expresses the polypeptide.

In another aspect, the present invention provides vectors comprising a nucleic acid encoding a polypeptide of the invention or a portion thereof. Examples of vectors include, but are not limited to,

5   plasmids, viral vectors, non-episomal mammalian vectors and expression vectors, for example, recombinant expression vectors.

The recombinant expression vectors of the invention can comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. The recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression,

10   which is operably linked to the nucleic acid sequence to be expressed. Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cells (*e.g.*, SV40 early gene enhancer, Rous sarcoma virus promoter and cytomegalovirus promoter), those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences, see Voss *et al.*, 1986, Trends Biochem. Sci. 11:287, Maniatis *et al.*, 1987, Science 236:1237, incorporated by reference

15   herein in their entireties), and those that direct inducible expression of a nucleotide sequence in response to particular treatment or condition (*e.g.*, the metallothionin promoter in mammalian cells and the tet-responsive and/or streptomycin responsive promoter in both prokaryotic and eukaryotic systems (see *id.*). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, *etc.* The

20   expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

In another aspect, the present invention provides host cells into which a recombinant expression vector of the invention has been introduced. A host cell can be any prokaryotic cell (for example, *E. coli*) or eukaryotic cell (for example, yeast, insect, or mammalian cells (*e.g.*, CHO cells)). Vector DNA can be

25   introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable

30   markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die), among other methods.

Indications

35   In one aspect, the present invention provides methods of treating a subject. The method can, for example, have a generally salubrious effect on the subject, *e.g.*, it can increase the subject's expected longevity. Alternatively, the method can, for example, treat, prevent, cure, relieve, or ameliorate ("treat") a disease, disorder, condition, or illness ("a condition"). Among the conditions to be treated in accordance with the present invention are conditions characterized by inappropriate expression or activity of IGF-1,

40   IGF-2, and/or IGF-1R. In some such conditions, the expression or activity level is too high, and the

treatment comprises administering an IGF-1R antagonist as described herein. In other such conditions, the expression or activity level is too low, and the treatment comprises administering an IGF-1R agonist as described herein.

One example of a type of condition that can be treated using the methods and compositions of the

5   present invention is a condition that involves cell growth, for example, a cancerous condition. Thus, in one embodiment, the present invention provides compositions and methods for treating a cancerous condition. The cancerous condition can be any cancerous condition that can be treated using the compositions comprised herein, for example, IGF-1R antagonizing antigen binding proteins such as anti-IGF-1R antibodies, antibody fragments, or antibody derivatives. Examples of cancerous conditions include, for

10   example, Acute Lymphoblastic Leukemia, Adrenocortical Carcinoma, AIDS-Related Cancers, AIDS-Related Lymphoma, Anal Cancer, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Basal Cell Carcinoma, Extrahepatic Bile Duct Cancer, Bladder Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma Bone Cancer, Brain Tumors (e.g., Brain Stem Glioma, Cerebellar Astrocytoma, Cerebral Astrocytoma/Malignant Glioma, Ependymoma, Medulloblastoma, Supratentorial Primitive

15   Neuroectodermal Tumors, Visual Pathway and Hypothalamic Glioma), Breast Cancer, Bronchial Adenomas/Carcinoids, Burkitt's Lymphoma, Carcinoid Tumor, Gastrointestinal Carcinoid Tumor, Carcinoma of Unknown Primary, Primary Central Nervous System, Cerebellar Astrocytoma, Cerebral Astrocytoma/Malignant Glioma, Cervical Cancer, Childhood Cancers, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Chronic Myeloproliferative Disorders, Colon Cancer, Colorectal Cancer,

20   Cutaneous T-Cell Lymphoma, Endometrial Cancer, Ependymoma, Esophageal Cancer, Ewing's Family of Tumors, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Intraocular Melanoma Eye Cancer, Retinoblastoma Eye Cancer, Gallbladder Cancer, Gastric (Stomach) Cancer, Gastrointestinal Carcinoid Tumor, Germ Cell Tumors (e.g., Extracranial, Extragonadal, and Ovarian), Gestational Trophoblastic Tumor, Glioma (e.g., Adult, Childhood Brain Stem, Childhood

25   Cerebral Astrocytoma, Childhood Visual Pathway and Hypothalamic), Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular (Liver) Cancer, Hodgkin's Lymphoma, Hypopharyngeal Cancer, Hypothalamic and Visual Pathway Glioma, Intraocular Melanoma, Islet Cell Carcinoma (Endocrine Pancreas), Kaposi's Sarcoma, Kidney (Renal Cell) Cancer, Laryngeal Cancer, Leukemia (e.g., Acute Lymphoblastic, Acute Myeloid, Chronic Lymphocytic, Chronic Myelogenous, and Hairy Cell), Lip and

30   Oral Cavity Cancer, Liver Cancer, Non-Small Cell Lung Cancer, Small Cell Lung Cancer, Lymphoma (e.g., AIDS-Related, Burkitt's, Cutaneous T-Cell, Hodgkin's, Non-Hodgkin's, and Primary Central Nervous System), Waldenström's Macroglobulinemia, Malignant Fibrous Histiocytoma of Bone/Osteosarcoma, Medulloblastoma, Melanoma, Intraocular (Eye) Melanoma, Merkel Cell Carcinoma, Mesothelioma, Metastatic Squamous Neck Cancer with Occult Primary, Multiple Endocrine Neoplasia Syndrome, Multiple

35   Myeloma/Plasma Cell Neoplasm, Mycosis Fungoides, Myelodysplastic Syndromes, Myelodysplastic/Myeloproliferative Diseases, Myelogenous Leukemia, Chronic Myeloid Leukemia, Multiple Myeloma, Chronic Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Oral Cancer, Oropharyngeal Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Cancer, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor,

40   Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Islet Cell Pancreatic Cancer, Paranasal Sinus

and Nasal Cavity Cancer, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pineoblastoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Pleuropulmonary Blastoma, Primary Central Nervous System Lymphoma, Prostate Cancer, Rectal Cancer, Renal Cell (Kidney) Cancer, Renal Pelvis and Ureter Transitional Cell Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Soft Tissue

5   Sarcoma, Uterine Sarcoma, Sezary Syndrome, non-Melanoma Skin Cancer, Merkel Cell Skin Carcinoma, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Cell Carcinoma, Cutaneous T-Cell Lymphoma, Testicular Cancer, Thymoma, Thymic Carcinoma, Thyroid Cancer, Gestational Trophoblastic Tumor, Carcinoma of Unknown Primary Site, Cancer of Unknown Primary Site, Urethral Cancer, Endometrial Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar

10 Cancer, Waldenström's Macroglobulinemia, and Wilms' Tumor.

Four different groups have studied a total of 425 breast cancers, mostly ductal in origin, and 48 normal tissues or benign specimens by radioimmunoassay ("RIA") or immunohistochemistry ("IHC") (Papa et al., 1993, Cancer Research 53: 3736-40, Happerfield et al., 1997, Journal of Pathology 183: 412-17; Ellis et al., 1998, Breast Cancer Research & Treatment 52: 175-84, Lee et al., 1998, Breast Cancer

15 Research & Treatment 47: 295-302, Schnarr et al., 2000, International Journal of Cancer 89: 506-13). These studies suggest that elevated IGF-1R expression, on the order of 5-10 fold, is associated with favorable prognosis and biomarkers (ER+ PR+), suggesting that estrogen and IGF cooperate in the maintenance or progression of well differentiated tumor. Similarly, estrogen has been shown to be essential for the growth and survival of the ER+ MCF-7 breast cancer cell line, and in this context IGF-1R is up-

20 regulated by estrogen treatment (reviewed in Ellis et al., 1998, Breast Cancer Research & Treatment 52: 175-84). Thus, in one embodiment, the present invention provides a method of treating breast cancer in a subject in need of such treatment, comprising administering to the subject an effective amount of an IGF-1R antagonist as described herein. In another embodiment, the method further comprises administering a hormone inhibitor, e.g., an estrogen inhibitor.

25 A retrospective IGF-1R IHC analysis has been reported for a collection of 12 colonic adenomas, 36 primary colorectal adenocarcinomas and 27 corresponding metastases, and 34 adjacent normal tissues (Hakam et al., 1999, Human Pathology. 30: 1128-33). The frequency of moderate to strong IHC staining appeared to dramatically increase with higher stage and tumor grade (0% normal vs. 93 % metastases). The results are consistent with RNA analysis by RNAse protection assay ("RPA") (Freier et al., 1999, Gut 44:

30 704-08). Thus, in one embodiment, the present invention provides a method of treating colon cancer in a subject in need of such treatment, comprising administering to the subject an effective amount of an IGF-1R antagonist as described herein.

High plasma IGF-1 and reduced IGFbp3 in men 40-80 years old is associated with increased prostate cancer risk (Chan et al., 1998, Science 279: 563-6). High IGF-1 is associated with a risk of other

35 cancers including breast (Hankinson et al., 1998, Lancet 351: 1393-96), colon (Ma et al., 1999, Journal of the National Cancer Institute 91: 620-25) and lung (Yu et al., 1999, Journal of the National Cancer Institute 91: 151-56). In transgenic mouse models, tumor incidence is increased by IGF-1 overexpression in diverse locations (Bol et al., 1997, Oncogene 14: 1725-34; DiGiovanni et al., 2000, Cancer Research 60: 1561-70; DiGiovanni et al., 2000, Proceedings of the National Academy of Sciences of the United States of America

40 97: 3455-60, Hadsell et al., 2000, Oncogene 19: 889-98). These mouse studies point to a role for both

serum and stromal produced IGF-1. Thus, in one embodiment, the present invention provides a method of treating a subject in need of such treatment, comprising administering to the subject an effective amount of an antagonist of IGF-1R as described herein, wherein the antagonist inhibits the activation of IGF-1R by IGF-1. In another embodiment, the subject has cancer. In another embodiment, the subject has a tumor. In
5   another embodiment, the cancer is prostate, breast, colon or lung cancer.

It has been observed that bone is the major source of IGF-1 in the body. Thus, in one aspect, the present invention provides compositions and methods for inhibiting IGF-1R in a bone of a subject. In one embodiment, an IGF-1R inhibitor of the present invention is administered to a subject that has, or is at risk for developing, a tumor in a bone. The tumor can be, for example, a primary tumor or a metastatic tumor.
10   The treatment optionally further comprises administering to the subject one or more additional therapeutic and/or palliative treatments, for example, an anti-tumor treatment (e.g., chemotherapy, radiation therapy, or anti-hormone therapy) or a treatment that inhibits bone turnover (e.g., denosumab (Amgen Inc., Thousand Oaks, CA)).

IGF-2 is overexpressed in a variety of tumors and stromal tissues. IGF-2 levels appear especially
15   high (as much as 40 fold) in primary liver cancers (Cariani et al., 1988, Cancer Research 48: 6844-49) and adenocarcinoma of the colon (Freier et al., 1999, Gut 44: 704-08). Many of the overgrowth disorders are associated with an increased incidence of childhood tumors. Five to ten percent of individuals with either the prenatal growth disorder Beckwith-Weidmann Syndrome (BWS) or hemihyperplasia develop tumors such as nephroblastoma, adrenal carcinoma, and neuroblastoma (reviewed by Morison et al., 1998,
20   Molecular Medicine Today 4: 110-05). The tumor-predisposing factor in these children appears to be the mosaic loss of maternal IGF-2 gene imprinting, or duplication of the paternal chromosomal arm (11p) that carries IGF-2. Both alterations would increase the level of IGF-2 expression. IGF-2 overexpression as a result of mosaic uniparental disomy or loss of IGF-2 imprinting has also been detected in Wilms tumors. Growth disorders are not observed in these children even though the IGF-2 gene alterations also occur in
25   some normal tissues, perhaps reflecting the tissue distribution of the affected cells. Imprinting of the maternal IGF-2 gene also occurs in mice, and the effects of IGF-2 overexpression are consistent with the human situation (Cariani et al., 1991, Journal of Hepatology 13: 220-26, Schirmacher et al., 1992, Cancer Research 52: 2549-56; Harris et al., 1998, Oncogene 16: 203-09). The incidence of tumors and organomegaly increases in mice that transgenically express excess IGF-2 (Christofori et al., 1994, Nature
30   369: 414-18, Ward et al., 1994, Proceedings of the National Academy of Sciences of the United States of America 91: 10365-9, Wolf et al., 1994, Endocrinology 135: 1877-86, Bates et al., 1995, British Journal of Cancer 72: 1189-93, Hassan et al., 2000, Cancer Research 60: 1070-76). Local IGF-2 overexpression increases the spontaneous appearance of prostate, mammary, intestinal, liver and epidermal tumors. Plasma specific expression using liver promoters elevate hepatocellular carcinomas and lymphoma. Thus, in one
35   embodiment, the present invention provides a method of treating a subject in need of such treatment, comprising administering to the subject an effective amount of an antagonist of IGF-1R as described herein, wherein the antagonist inhibits the activation of IGF-1R by IGF-2. In another embodiment, the subject has cancer. In another embodiment, the subject has a tumor. In another embodiment, the subject has liver cancer, adenocarcinoma of the colon, Beckwith-Weidmann Syndrome, hemihyperplasia, nephroblastoma,
40   adrenal carcinoma, neuroblastoma, mosaic loss of maternal IGF-2 gene imprinting, duplication of the

paternal chromosomal arm (11p), increased IGF-2 expression, a tumor (*e.g.*, a prostate, mammary, intestinal, liver, epidermal, or Wilms tumor), organomegaly, hepatocellular carcinoma, or lymphoma.

In another aspect, the invention provides methods of preventing or inhibiting a cancer from spreading to another part of the body, or of treating a cancer that has spread to another part of the body. In one embodiment, the cancer has spread to a regional lymph node. In another embodiment, the cancer is metastatic. The primary tumor can be any kind of tumor, for example, an adenocarcinoma tumor (*e.g.*, a prostate adenocarcinoma tumor, a breast carcinoma tumor, or a renal cell carcinoma tumor), a non-small cell or small cell lung cancer tumor, a thyroid cancer tumor, *etc.* The site of the metastatic tumor can be anywhere in the body. It can be, for example, in bone, the lymph system, lung, brain, eye, skin, pancrease, or liver. In one particular embodiment, a subject having a tumor disease is treated with an effective amount of an IGF-1R inhibiting composition of the present invention such that the primary tumor is prevented from metastasizing. In another particular embodiment, a subject having a primary tumor is treated with an effective amount of an IGF-1R inhibiting composition of the present invention such that the primary tumor is inhibited from metastasizing. In another particular embodiment, a subject having a metastatic tumor is treated with an effective amount of an IGF-1R inhibiting composition of the present invention such that growth or spreading of the secondary tumor is inhibited. In another particular embodiment, a subject having a metastatic tumor is treated with an effective amount of an IGF-1R inhibiting composition of the present invention such that the secondary tumor is reduced in size. In a more particular embodiment, the primary tumor is an adenocarcinoma tumor, a non-small cell lung tumor, a small cell lung tumor, or a thyroid cancer. In another more particular embodiment, the metastatic tumor is in a bone. In another more particular embodiment, a metastatic tumor is prevented or inhibited from forming in a bone. In another more particularly defined embodiment, the method comprises treating the subject with an IGF-1R inhibiting composition of the present invention and one or more other treatments (e.g., a treatment that kills or inhibits the growth of cancer cells, such as radiation, hormonal therapy, or chemotherapy, or a treatment that inhibits the turnover of bone, such as denosumab), non-limiting examples of which are provided herein. The one or more other treatments can include, for example the standard of care for the subject's particular condition and/or palliative care.

Without being bound to any particular theory, tumor cells appear to depend on the PI3 Kinase/Akt signaling pathway to resist the apoptosis-inducing activity of chemotherapeutics, radiation, and anti-hormone therapy. Thus, in one embodiment, the present invention provides methods of treating a subject in need of such treatment comprising administering to the subject an IGF-1R antagonist of the present invention and a chemotherapeutic, radiation, and/or an anti-hormone therapy. This concept has been validated experimentally in cell culture models and rodent tumor models by antisense and dominant negative mutations (reviewed by Baserga *et al.*, 1997, Biochimica et Biophysica Acta 1332: F105-26, Baserga, 2000, Oncogene 19: 5574-81). In one embodiment, the chemotherapeutic agents is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, anti-survival agents, biological response modifiers, anti-hormones, e.g. anti-androgens, and anti-angiogenesis agents.

One example of a chemotherapeutic agent that can be administered in combination with an IGF-1 receptor inhibitor of the invention is CPT-11. CPT-11 (Irinotecan hydorchloride trihydrate) is a semi

synthetic, water soluble derivative of camptothecin, a plant alkaloid. CPT-11 and an associated metabolite called SN38 inhibit topoisomerase 1 (TOPO1). This enzyme introduces reversible single-strand breaks in DNA that allow unwinding and permit DNA replication to proceed. Inhibition of TOPO1 prevents religation of single-strand breaks after DNA replication resulting in greatly increased chromosomal
5   fragmentation. This DNA damage promotes cell death by apoptosis through the action of p53 and other systems that monitor genome integrity. The cytotoxic effect of CPT-11 is generally limited to cells that are replicating DNA (S-Phase). Quiescent cells are largely unaffected.

In another embodiment, the present invention provides treating a subject in need thereof with an effective amount of an IGF-1R antagonist of the present invention and with an effective amount of an
10   apoptosis-inducing agent.

In another embodiment, an anti-angiogenesis agent, such as an MMP-2 (matrix-metalloproteinase 2) inhibitor, an MMP-9 (matrix-metalloproteinase 9) inhibitor, and/or a COX-II (cyclooxygenase II) inhibitor, is used in conjunction with a compound of the invention. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), BEXTRA™ (valdecoxib), and VIOXX™ (rofecoxib). Examples of
15   useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published Oct. 24, 1996), WO 96/27583 (published Mar. 7, 1996), European Patent Application No. 97304971.1 (filed Jul. 8, 1997), European Patent Application No. 99308617.2 (filed Oct. 29, 1999), WO 98/07697 (published Feb. 26, 1998), WO 98/03516 (published Jan. 29, 1998), WO 98/34918 (published Aug. 13, 1998), WO 98/34915 (published Aug. 13, 1998), WO 98/33768 (published Aug. 6, 1998), WO 98/30566 (published Jul. 16,
20   1998), European Patent Publication 606,046 (published Jul. 13, 1994), European Patent Publication 931,788 (published Jul. 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published Oct. 21, 1999), WO 99/52889 (published Oct. 21, 1999), WO 99/29667 (published Jun. 17, 1999), PCT International Application No. PCT/IB98/01113 (filed Jul. 21, 1998), European Patent Application No. 99302232.1 (filed Mar. 25, 1999), Great Britain patent application number 9912961.1 (filed Jun. 3, 1999),
25   U.S. Provisional Application No. 60/148,464 (filed Aug. 12, 1999), U.S. Pat. No. 5,863,949 (issued Jan. 26, 1999), U.S. Pat. No. 5,861,510 (issued Jan. 19, 1999), and European Patent Publication 780,386 (published Jun. 25, 1997), all of which are incorporated herein in their entireties by reference. In one embodiment, the MMP inhibitor is one that does not demonstrate arthralgia. In another embodiment, the MMP inhibitor selectively inhibits MMP-2 and/or MMP-9 relative to other matrix-metalloproteinases (i.e., MMP-1, MMP-
30   3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13). Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list: 3-[[4-(4-fluoro-phenoxy)-benzene- sulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid; 3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]o- ctane-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(2-
35   chloro-4-fluoro-ben- zyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-py- ran-4-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfon- yl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid; 4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxyl- ic acid hydroxyamide; (R) 3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-te- trahydro-pyran-3-carboxylic acid
40   hydroxyamide; (2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-pi-

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peridine-2-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenes- ulfonyl]-(1-

hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-

hydroxycarbamoyl-tetrahydro-- pyran-4-yl)-amino]-propionic acid; 3-exo-3-[4-(4-chloro-phenoxy)-

benzenesu- lfonylamino]-8-oxa-icyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; 3-endo-3-[4-(4-

5   fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-icyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and

(R) 3-[4-(4-fluoro-phenoxy)-b- enzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide;

and pharmaceutically acceptable salts, solvates, derivatives, and other preparations of the compounds.

Sporadic mutations that inactivate the PETN gene product occur relatively frequently in most

human cancers (Yamada *et al.*, 2001, J Cell Sci 114:2375-82, Hill *et al.*, 2002, Pharmacol Therapeut

10   93:243-51). Loss of PTEN causes the Akt phosphorylated state to persist through loss of the ability to

down-regulate stimulatory signals originating from IGF-1R and other sources. The status of the p53 tumor

suppressor also influences the activity of the IGF-1R signaling system. In the ground state, the basal or

constitutive transcription of IGF-1R is repressed by p53 via an indirect mechanism. Activation of Akt

promotes the phosphorylation of mdm2, which then binds the p53 tumor suppressor and promotes its

15   degradation (Mayo *et al.*, 2002, TIBS 27:462-67), resulting in increased IGF-1R expression. A similar

outcome is observed when p53 is inactivated by mutation. When transiently expressed in Saos-2 (a human

osteosarcoma cell line) and RD (a rhabdomyosarcoma cell line), wild-type p53 is able to suppress the

activity of a cotransfected IGF-1R promoter construct, whereas tumor-derived, mutant versions of p53 have

no effect. It has been proposed that the increased level of IGF-1R promotes the resistance to apoptosis

20   associated with p53 loss in malignant cells (Werner *et al.*, 2000, Cell Mol Life Sci 57:932-42). Thus, in one

embodiment, the present invention provides a method of treating a cancerous condition in a subject in need

of such treatment comprising administering to the subject an effective amount of an IGF-1R antagonist as

described herein, wherein the cancerous condition is characterized by cells that have a reduced expression

or activity of p53.

25   The WT1 (Wilms kidney tumor suppressor 1 protein) also has been shown to bind and repress the

IGF-1R promoter. Thus, in one embodiment, the present invention provides a method of treating a

cancerous condition in a subject in need of such treatment comprising administering to the subject an

effective amount of an IGF-1R antagonist as described herein wherein the cancerous condition is

characterized by a reduced expression or activity of WT1.

30   The proliferation of normal fibroblasts has been shown to require, under defined culture

conditions, the combined action of IGF and a stromal growth factor (*e.g.* PDGF, EGF) to ramp-up

Ras/Raf/Map Kinase and promote cell cycle entry (the G0 to G1 transition). Fibroblasts derived from IGF-

1R (-/-) mice do not respond to growth factor alone, or most oncogenes (*e.g.* oncogenic Ras) that activate

the Ras/Raf/Map Kinase pathway. Thus, in one embodiment, the present invention provides a method of

35   treating a subject in need of such treatment comprising administering to the subject an IGF-1R antagonist as

described herein and an agent that targets a growth factor and/or a growth factor receptor, such as a growth

factor receptor tyrosine kinase, *e.g.*, the EGFR, HER-2, bcr-abl, VEGFR, Kit, raf, mTOR, CDK1/2,

VEGFR2, PKCβ, Mek, and/or KDR. Examples of molecules that target such growth factors and/or

receptors include panitumumab (Abgenix, Fremont, CA/Amgen, Thousand Oaks, CA), HERCEPTIN™

40   (Genentech, South San Francisco, CA), GLEEVEC™ (Novartis, East Hanover, NJ), IRESSA™

(AstraZeneca, Wilmington, DE), ERBITUX™, (ImClone, New York, NY), AVASTIN™, (Genentech), PTK787 (Novartis), SU11248 (Pfizer, New York, NY), TARCEVA™ (OSI Pharmaceuticals, Melville, NY), 43-9006 (Bayer, West Haven, CT), CCI-779 (Wyeth, Madison, NJ), RAD001 (Novartis), BMS-387032 (Bristol-Myers Squibb, New York, NY), IMC-1C11 (ImClone), LY333531 (Eli Lilly, Indianapolis,

5   IN), PD 184352 (Pfizer), 2C4 (Genentech), and GW2016 (GlaxoSmithKline, Research Triangle Park, NC).

The role of IGF-1R in hematological malignancies has been reviewed by (Novak *et al.*, 2003, *Insulin-Like Growth Factors and Hematological Malignancies* in Insulin-Like Growth Factors, LeRoith *et al.*, ed.s, Landes Bioscience). A functional role for the IGF-1R in hematopoietic malignancies is demonstrated by, for example, the ability of IGF-1R monoclonal antibodies to block transformed cell

10   growth in culture. IGF-I has been found to enhance growth of freshly isolated human acute myelogenous leukemia and acute lymphoblastic leukemia blasts. With respect to T cell malignancies, IGF-I has been shown to influence the growth of murine lymphoma cells bearing a pre-T cell phenotype and, immature and mature primary human T lineage acute lymphoblastic leukemia cells were found to express high numbers of IGF-1R. Thus, in one embodiment, the present invention provides methods of treating a hematological

15   malignancy in a subject in need thereof comprising administering to the subject an antagonist of IGF-1R as described herein. In another embodiment, the malignancy is an acute myelogenous leukemia, an acute lymphoblastic leukemia, or a T cell malignancy.

In another aspect, the present invention provides methods of identifying subjects who are more likely to benefit from treatment using the compositions and/or methods of treatment of the present

20   invention. Such methods can enable a caregiver to better tailor a therapeutic regimen to a particular subject's needs and reduce the likelihood of an ineffective or counterproductive course of treatment. In one embodiment, the present invention provides a method of determining whether a subject is a candidate for treatment using a composition or method as described herein comprising determining whether a target cell type in the subject expresses IGF-1R, wherein if the target cell type expresses IGF-1R, then the subject is a

25   candidate for treatment. In another embodiment, the method comprises determining the approximate average number of IGF-1R molecules per target cell, wherein 10^2, 10^3, 10^4, 10^5, or 10^6 IGF-1R per cell indicates that the subject is a candidate for treatment. The approximate average number of IGF-1R molecules per target cell can be determined using any technique known in the art, for example, by staining a sample comprising cells of the target cell type with an IGF-1R binding molecule, and detecting the amount

30   of IGF-1R binding molecule bound to the sample, where the amount of IGF-1R binding molecule detected is proportional to the average number of IGF-1R molecules in the sample. In another embodiment, the method comprises comparing the approximate average number of IGF-1R molecules per target cell to a reference standard, wherein if the approximate average number of IGF-1R molecules per target cell is greater than the reference standard, then the subject is more likely to benefit from treatment using the

35   compositions and/or methods of treatment of the present invention. In another embodiment, the target cell type is a cancerous cell type. In another embodiment, the target cell type is a colon cancer cell type, a breast cancer cell type, an NSCLC cell type, or a leukemic cell type.

In another embodiment, a subject who is a candidate for treatment is identified by detecting IGF-1 and/or IGF-2 in the target cell type, or in the stratum of the target cell type. In another embodiment, the

target cell type is a cancerous cell type. In another embodiment, the target cell type is a colon cancer cell type, a breast cancer cell type, an NSCLC cell type, or a leukemic cell type.

In another embodiment, a subject who is a candidate for treatment is identified by detecting activity of IGF-1R-mediated signaling in the target cell type, wherein IGF-1R-mediated signaling in the
5   target cell type indicates that the subject is a candidate for treatment. Examples of molecules that can be monitored for IGF-1R-dependent changes are shown in Figure 10, such as molecules in the PI3/Akt pathway, *e.g.*, IGF-1R, IRS adapters, Akt, *etc.* Such molecules can be monitored for, for example, a change in phosphorylation status, *e.g.*, an increase in phosphorylation. Phosphospecific antibodies that recognize the activated forms of these protein markers are highly developed, and these reagents have proven to be
10   reliable for immunoblot detection in experimental systems.

The compositions and/or methods of the present invention also can be used, for example, in cosmetic treatments, in veterinary treatments, to increase longevity, to treat reproductive defects, and to treat a variety of growth related disorders.

15   Therapeutic methods and administration of antigen binding proteins

Certain methods provided herein comprise administering an IGF-1R binding antigen binding protein to a subject, thereby reducing an IGF-1-induced biological response that plays a role in a particular condition. In particular embodiments, methods of the invention involve contacting endogenous IGF-1R with an IGF-1R binding antigen binding protein, *e.g.*, via administration to a subject or in an *ex vivo*
20   procedure.

The term "treatment" encompasses alleviation or prevention of at least one symptom or other aspect of a disorder, or reduction of disease severity, and the like. An antigen binding protein need not effect a complete cure, or eradicate every symptom or manifestation of a disease, to constitute a viable therapeutic agent. As is recognized in the pertinent field, drugs employed as therapeutic agents may reduce
25   the severity of a given disease state, but need not abolish every manifestation of the disease to be regarded as useful therapeutic agents. Similarly, a prophylactically administered treatment need not be completely effective in preventing the onset of a condition in order to constitute a viable prophylactic agent. Simply reducing the impact of a disease (for example, by reducing the number or severity of its symptoms, or by increasing the effectiveness of another treatment, or by producing another beneficial effect), or reducing the
30   likelihood that the disease will occur or worsen in a subject, is sufficient. One embodiment of the invention is directed to a method comprising administering to a patient an IGF-1R antagonist in an amount and for a time sufficient to induce a sustained improvement over baseline of an indicator that reflects the severity of the particular disorder.

As is understood in the pertinent field, pharmaceutical compositions comprising the molecules of
35   the invention are administered to a subject in a manner appropriate to the indication. Pharmaceutical compositions may be administered by any suitable technique, including but not limited to parenterally, topically, or by inhalation. If injected, the pharmaceutical composition can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal or subcutaneous routes, by bolus injection, or continuous infusion. Localized administration, *e.g.* at a site of disease or injury is
40   contemplated, as are transdermal delivery and sustained release from implants. Delivery by inhalation

includes, for example, nasal or oral inhalation, use of a nebulizer, inhalation of the antagonist in aerosol form, and the like. Other alternatives include eyedrops; oral preparations including pills, syrups, lozenges or chewing gum; and topical preparations such as lotions, gels, sprays, and ointments.

5   Use of antigen binding proteins in *ex vivo* procedures also is contemplated. For example, a patient's blood or other bodily fluid may be contacted with an antigen binding protein that binds IGF-1R *ex vivo*. The antigen binding protein may be bound to a suitable insoluble matrix or solid support material.

Advantageously, antigen binding proteins are administered in the form of a composition comprising one or more additional components such as a physiologically acceptable carrier, excipient or diluent. Optionally, the composition additionally comprises one or more physiologically active agents, for

10   example, a second IGF-1 receptor-inhibiting substance, an anti-angiogenic substance, a chemotherapeutic substance, an analgesic substance, *etc.*, non-exclusive examples of which are provided herein. In various particular embodiments, the composition comprises one, two, three, four, five, or six physiologically active agents in addition to an IGF-1R binding antigen binding protein

In one embodiment, the pharmaceutical composition comprise an antigen binding protein of the

15   invention together with one or more substances selected from the group consisting of a buffer, an antioxidant such as ascorbic acid, a low molecular weight polypeptide (such as those having fewer than 10 amino acids), a protein, an amino acid, a carbohydrate such as glucose, sucrose or dextrins, a chelating agent such as EDTA, glutathione, a stabilizer, and an excipient. Neutral buffered saline or saline mixed with conspecific serum albumin are examples of appropriate diluents. In accordance with appropriate

20   industry standards, preservatives such as benzyl alcohol may also be added. The composition may be formulated as a lyophilizate using appropriate excipient solutions (*e.g.*, sucrose) as diluents. Suitable components are nontoxic to recipients at the dosages and concentrations employed. Further examples of components that may be employed in pharmaceutical formulations are presented in Remington's Pharmaceutical Sciences, 16th Ed. (1980) and 20th Ed. (2000), Mack Publishing Company, Easton, PA.

25   Kits for use by medical practitioners include an IGF-1 receptor-inhibiting substance of the invention and a label or other instructions for use in treating any of the conditions discussed herein. In one embodiment, the kit includes a sterile preparation of one or more IGF-1R binding antigen binding proteins, which may be in the form of a composition as disclosed above, and may be in one or more vials.

Dosages and the frequency of administration may vary according to such factors as the route of

30   administration, the particular antigen binding proteins employed, the nature and severity of the disease to be treated, whether the condition is acute or chronic, and the size and general condition of the subject. Appropriate dosages can be determined by procedures known in the pertinent art, *e.g.* in clinical trials that may involve dose escalation studies.

An IGF-1 receptor inhibiting substance of the invention may be administered, for example, once or

35   more than once, *e.g.*, at regular intervals over a period of time. In particular embodiments, an antigen binding protein is administered over a period of at least a month or more, *e.g.*, for one, two, or three months or even indefinitely. For treating chronic conditions, long-term treatment is generally most effective. However, for treating acute conditions, administration for shorter periods, *e.g.* from one to six weeks, may be sufficient. In general, the antigen binding protein is administered until the patient manifests a medically

40   relevant degree of improvement over baseline for the chosen indicator or indicators.

Particular embodiments of the present invention involve administering an antigen binding protein at a dosage of from about 1 ng of antigen binding protein per kg of subject's weight per day ("1ng/kg/day") to about 10 mg/kg/day, more preferably from about 500 ng/kg/day to about 5 mg/kg/day, and most preferably from about 5 µg/kg/day to about 2 mg/kg/day, to a subject. In additional embodiments, an

5   antigen binding protein is administered to adults one time per week, two times per week, or three or more times per week, to treat an IGF-1 and/or IGF-2 mediated disease, condition or disorder, e.g., a medical disorder disclosed herein. If injected, the effective amount of antigen binding protein per adult dose may range from 1-20 mg/m², and preferably is about 5-12 mg/m². Alternatively, a flat dose may be administered; the amount may range from 5-100 mg/dose. One range for a flat dose is about 20-30 mg per

10   dose. In one embodiment of the invention, a flat dose of 25 mg/dose is repeatedly administered by injection. If a route of administration other than injection is used, the dose is appropriately adjusted in accordance with standard medical practices. One example of a therapeutic regimen involves injecting a dose of about 20-30 mg of antigen binding protein to one to three times per week over a period of at least three weeks, though treatment for longer periods may be necessary to induce the desired degree of

15   improvement. For pediatric subjects (age 4-17), one exemplary suitable regimen involves the subcutaneous injection of 0.4 mg/kg, up to a maximum dose of 25 mg of antigen binding protein administered two or three times per week.

Particular embodiments of the methods provided herein involve subcutaneous injection of from 0.5 mg to 10 mg, preferably from 3 to 5 mg, of an antigen binding protein, once or twice per week. Another

20   embodiment is directed to pulmonary administration (e.g., by nebulizer) of 3 or more mg of antigen binding protein once a week.

Examples of therapeutic regimens provided herein comprise subcutaneous injection of an antigen binding protein once a week, at a dose of 1.5 to 3 mg, to treat a condition in which IGF-1R signaling plays a role. Examples of such conditions are provided herein and include, for example, cancer, acromegaly and

25   other overgrowth disorders, diabetes, obesity, macular degeneration, and aging. Weekly administration of antigen binding protein is continued until a desired result is achieved, e.g., the subject's symptoms subside. Treatment may resume as needed, or, alternatively, maintenance doses may be administered.

Other examples of therapeutic regimens provided herein comprise subcutaneous or intravenous administration of a dose of 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 15, or 20 milligrams of an IGF-1R inhibitor of the

30   present invention per kilogram body mass of the subject (mg/kg). The dose can be administered once to the subject, or more than once at a certain interval, for example, once a day, three times a week, twice a week, once a week, three times a month, twice a month, once a month, once every two months, once every three months, once every six months, or once a year. The duration of the treatment, and any changes to the dose and/or frequency of treatment, can be altered or varied during the course of treatment in order to meet the

35   particular needs of the subject.

In another embodiment, an antigen binding protein is administered to the subject in an amount and for a time sufficient to induce an improvement, preferably a sustained improvement, in at least one indicator that reflects the severity of the disorder that is being treated. Various indicators that reflect the extent of the subject's illness, disease or condition may be assessed for determining whether the amount and time of the

40   treatment is sufficient. Such indicators include, for example, clinically recognized indicators of disease

severity, symptoms, or manifestations of the disorder in question. In one embodiment, an improvement is considered to be sustained if the subject exhibits the improvement on at least two occasions separated by two to four weeks. The degree of improvement generally is determined by a physician, who may make this determination based on signs, symptoms, biopsies, or other test results, and who may also employ
5   questionnaires that are administered to the subject, such as quality-of-life questionnaires developed for a given disease.

Elevated levels of IGF-1 and/or IGF-2 are associated with a number of disorders, including, for example, cancer (*e.g.*, lung, prostate, breast and colon cancers), and acromegaly and other overgrowth disorders (*e.g.*, constitutionally tall children). Subjects with a given disorder may be screened, to identify
10   those individuals who have elevated IGF-1 and/or IGF-2 levels, thereby identifying the subjects who may benefit most from treatment with an IGF-1R binding antigen binding protein. Thus, treatment methods provided herein optionally comprise a first step of measuring a subject's IGF-1 and/or IGF-2 levels. An antigen binding protein may be administered to a subject in whom IGF-1 and/or IGF-2 levels are elevated above normal. In one embodiment, the present invention provides a method of treating an overgrowth
15   disorder (*e.g.*, acromegaly) comprising administering to a subject in need thereof an antigen binding protein of the present invention and pegvisomant.

A subject's levels of IGF-1 and/or IGF-2 may be monitored before, during and/or after treatment with an antigen binding protein, to detect changes, if any, in their levels. For some disorders, the incidence of elevated IGF-1 and/or IGF-2 levels may vary according to such factors as the stage of the disease or the
20   particular form of the disease. Known techniques may be employed for measuring IGF-1 and/or IGF-2 levels, *e.g.*, in a subject's serum. IGF-1 and/or IGF-2 levels in blood samples may be measured using any suitable technique, for example, ELISA.

Particular embodiments of methods and compositions of the invention involve the use of an antigen binding protein and one or more additional IGF-1R antagonists, for example, two or more antigen
25   binding proteins of the invention, or an antigen binding protein of the invention and one or more other IGF-1R antagonists. In further embodiments, antigen binding protein are administered alone or in combination with other agents useful for treating the condition with which the patient is afflicted. Examples of such agents include both proteinaceous and non-proteinaceous drugs. When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized in the pertinent art. "Co-
30   administration" and combination therapy are not limited to simultaneous administration, but also include treatment regimens in which an antigen binding protein is administered at least once during a course of treatment that involves administering at least one other therapeutic agent to the patient.

Examples of other agents that may be co-administered with an antigen binding protein are other antigen binding proteins or therapeutic polypeptides that are chosen according to the particular condition to
35   be treated. Alternatively, non-proteinaceous drugs that are useful in treating one of the particular conditions discussed above may be co-administered with an IGF-1R antagonist.

Combination therapy

In another aspect, the present invention provides a method of treating a subject with an IGF-1R
40   inhibiting antigen binding protein and one or more other treatments. In one embodiment, such a

52

combination therapy achieves synergy or an additive effect by, for example, attacking multiple sites or molecular targets in a tumor. Types of combination therapies that can be used in connection with the present invention include inhibiting or activating (as appropriate) multiple nodes in a single disease-related pathway, multiple pathways in a target cell, and multiple cell types within a target tissue (e.g., within a

5   tumor). For example, an IGF-1R inhibitor of the present invention can be combined with a treatment that inhibits IGF-1, promotes apoptosis, inhibits angiogenesis, or inhibits macrophage. In another embodiment, a targeted agent, that, when used by itself, fails to elicit a therapeutically desired effect, could be used to, for example, sensitize cancer cells or augment treatment effect of other agents. In another embodiment, an IGF-1R inhibitor according to the invention is used in combination with a cytotoxic drug or other targeted

10   agent that induces apoptosis. In another embodiment, an IGF-1R inhibitor is used in combination with one or more agents that inhibit different targets that are involved in cell survival (e.g., PKB, mTOR), different receptor tyrosine kinases (e.g., ErbB1, ErbB2, c-Met, c-kit), or different cell types (e.g., KDR inhibitors, c-fms). In another embodiment, an IGF-1R inhibitor of the invention is added to the existing standard of care for a particular condition. Examples of therapeutic agents include, but are not limited to, gemcitabine,

15   taxol, taxotere, and CPT-11.

In another embodiment, a combination therapy method comprises administering to the subject two, three, four, five, six, or more of the IGF-1R agonists or antagonists described herein. In another embodiment, the method comprises administering to the subject two or more treatments that together inhibit or activate (directly or indirectly) IGF-1R-mediated signal transduction. Examples of such methods include

20   using combinations of two or more IGF-1R inhibiting antigen binding progeins, of an IGF-1R inhibiting antigen binding protein and one or more other IGF-1, IGF-2, and/or IGF-1R agonists or antagonists (e.g., IGF-1 and/or IGF-2 binding polypeptides, IGF-1R binding polypeptides, IGF-1 and/or IGF-2 derivatives, anti-IGF-1 and/or IGF-2 antibodies, anti-sense nucleic acids against IGF-1, IGF-2, and/or IGF-1R, or other molecules that bind to IGF-1, IGF-2, and/or IGF-1R polypeptides or nucleic acids), or of an IGF-1R

25   inhibiting antigen binding protein and one or more other treatments (e.g., surgery, ultrasound, radiotherapy, chemotherapy, or treatment with another anti-cancer agent), as described, for example, in US Pat. No. 5,473,054 (issued Dec. 5, 1995), 6,051,593 (issued April 18, 2000), 6,084,085 (issued July 4, 2000), 6,506,763 (issued Jan. 14, 2003), US Pat. App. Pub. No.s 03/0092631 (published May 15, 2003), 03/0165502 (published Sept. 4, 2003), 03/0235582 (published Dec. 25, 2003), 04/0886503 (published May

30   6, 2004), 05/0272637 (published Dec. 8, 2005), PCT Pub. Ser. No.s WO 99/60023 (published Nov. 25, 1999), WO 02/053596 (published July 11, 2002), WO 02/072780 (published Sept. 19, 2002), WO 03/027246 (published March 3, 2003), WO 03/020698 (published March 13, 2003), WO 03/059951 (published July 24, 2003), WO 03/100008 (published Dec. 4, 2003), WO 03/106621 (published Dec. 24, 2003), WO 04/071529 (published August 26, 2004), WO 04/083248 (published Sept. 30, 2004), WO

35   04/087756 (published Oct. 14, 2004), WO 05/112969 (published Dec. 1, 2005), Kull et al., 1983, J Biol Chem 258:6561-66, Flier et al., 1986, Proc Natl Acad Sci USA 83:664-668, Conover et al., 1987, J Cell Physiol 133:560-66, Rohlik et al., 1987, Biochem Biophys Res Comm 149:276-81, Arteaga et al., 1989, J Clinical Investigation 84:1418-23, Arteaga et al., 1989, Cancer Res 49:6237-41, Gansler et al., 1989, American J Pathol 135:961-66, Gustafson et al., 1990, J Biol Chem 265:18663-67, Steele-Perkins et al.,

40   1990, Biochem Biophys Res Comm 171:1244-51, Cullen et al., 1992, Mol Endocrinol 6:91-100, Soos et

al., 1992, J Biol Chem 267:12955-63, Xiong *et al.*, 1992, Proc Natl Acad Sci USA 89:5356-60, Brunner *et al.*, 1993, Euro J Cancer 29A:562-69, Furlanetto *et al.*, 1993, Cancer Res 53:2522-26, Li *et al.*, 1993, Biochem Biophys Res Comm 196:92-98, Kalebic *et al.*, 1994, Cancer Res 54:5531-34, Lahm *et al.*, 1994, Intl J Cancer 58:452-59, Zia *et al.*, 1996, J Cell Biochem Supp 24:269-75, Jansson *et al.*, 1997, J Biol Chem

5   272:8189-97, Scotlandi *et al.*, 1998, Cancer Res 58:4127-31, Logie *et al.*, 1999, Li *et al.*, 2000, Cancer Immunol Immunotherapy 49:243-52, J Mol Endocrinol 23:23-32, De Meyts *et al.*, 2002, Nature Reviews 1:769-83, Hailey *et al.*, 2002, Mol Cancer Therapeutics 1:1349-53, Maloney *et al.*, 2003, Cancer Research 63:5073-83, Burtrum *et al.*, 2003, Cancer Research 63:8912-21, and Karavitaki *et al.*, 2004, Hormones 3:27-36, (each incorporated herein by reference in its entirety) may be employed in methods and

10   compositions of the present invention. Furthermore, one or more anti-IGF-1R antibodies or antibody derivatives can be used in combination with one or more molecules or other treatments, wherein the other molecule(s) and/or treatment(s) do not directly bind to or affect IGF-1R, IGF-1, or IGF-2, but which combination is effective for treating or preventing a condition, such as cancer or an overgrowth disorder (*e.g.*, acromegaly). In one embodiment, one or more of the molecule(s) and/or treatment(s) treats or

15   prevents a condition that is caused by one or more of the other molecule(s) or treatment(s) in the course of therapy, *e.g.*, nausea, fatigue, alopecia, cachexia, insomnia, *etc.* In every case where a combination of molecules and/or other treatments is used, the individual molecule(s) and/or treatment(s) can be administered in any order, over any length of time, which is effective, *e.g.*, simultaneously, consecutively, or alternately. In one embodiment, the method of treatment comprises completing a first course of

20   treatment with one molecule or other treatment before beginning a second course of treatment. The length of time between the end of the first course of treatment and beginning of the second course of treatment can be any length of time that allows the total course of therapy to be effective, *e.g.*, seconds, minutes, hours, days, weeks, months, or even years.

In another embodiment, the method comprises administering one or more of the IGF-1R

25   antagonists described herein and one or more other treatments (*e.g.*, a therapeutic or palliative treatment), for example, anti-cancer treatments (such as surgery, ultrasound, radiotherapy, chemotherapy, or treatment with another anti-cancer agent). Where a method comprises administering more than one treatment to a subject, it is to be understood that the order, timing, number, concentration, and volume of the administrations is limited only by the medical requirements and limitations of the treatment, *i.e.*, two

30   treatments can be administered to the subject, *e.g.*, simultaneously, consecutively, alternately, or according to any other regimen. Examples of agents that can be administered in combination with the IGF-1R antagonists described herein include, but are not limited to, neutrophil-boosting agents, irinothecan, SN-38, gemcitabine, herstatin, or an IGF-1R-binding herstatin derivative (as described, for example, in US Pat. App. No. 05/0272637), AVASTIN® (Genentech, South San Francisco, CA), HERCEPTIN® (Genentech),

35   RITUXAN® (Genentech), ARIMIDEX® (AstraZeneca, Wilmington, DE), IRESSA® (AstraZeneca), BEXXAR® (Corixa, Seattle, WA), ZEVALIN® (Biogen Idec, Cambridge, MA), ERBITUX® (Imclone Systems Inc., New York, NY), GEMZAR® (Eli Lilly and Co., Indianapolis, IN), CAMPTOSAR® (Pfizer, New York, NY), GLEEVEC® (Novartis), SU-11248 (Pfizer), BMS-354825 (Bristol-Myers Squibb), panitumumab (Abgenix, Fremont, CA/Amgen Inc., Thousand Oaks, CA), and denosumab (Amgen Inc.,

40   Thousand Oaks, CA).

The following examples, both actual and prophetic, are provided for the purpose of illustrating specific embodiments or features of the instant invention and do not limit its scope.

EXAMPLE 1: Preparation of Antibodies

5   This example demonstrates a method of preparing antibodies recognizing the IGF-1 receptor. IGF-1 receptor polypeptides may be employed as immunogens in generating monoclonal antibodies by conventional techniques. It is recognized that polypeptides in various forms may be employed as immunogens, e.g., full length proteins, fragments thereof, fusion proteins thereof such as Fc fusions, cells expressing the recombinant protein on the cell surface, etc.

10   To summarize an example of such a procedure, an IGF-1R immunogen emulsified in complete Freund's adjuvant is injected subcutaneously into Lewis rats, in amounts ranging from 10-100 μl. Three weeks later, the immunized animals are boosted with additional immunogen emulsified in incomplete Freund's adjuvant and boosted every three weeks thereafter. Serum samples are periodically taken by retro-orbital bleeding or tail-tip excision for testing by dot-blot assay, ELISA (enzyme-linked immunosorbent

15   assay), or inhibition of binding of ^{125}I-IGF-1 or ^{125}I-IGF-2 to extracts of IGF-1R-expressing cells. Following detection of an appropriate antibody titer, positive animals are given a final intravenous injection of antigen in saline. Three to four days later, the animals are sacrificed, splenocytes harvested, and fused to the murine myeloma cell line AG8653. The resulting hybridoma cell lines are plated in multiple microtiter plates in a HAT selective medium (hypoxanthine, aminopterin, and thymidine) to inhibit proliferation of

20   non-fused cells, myeloma hybrids, and spleen cell hybrids.

Hybridoma clones thus generated are screened for reactivity with IGF-1R. Initial screening of hybridoma supernatants utilizes an antibody capture and binding of partially purified ^{125}I-IGF-1 receptor. Hybridomas that are positive in this screening method are tested by a modified antibody capture to detect hybridoma cells lines that are producing blocking antibody. Hybridomas that secrete a monoclonal

25   antibody capable of inhibiting ^{125}I-IGF-1 binding to cells expressing IGF-1R are thus detected. Such hybridomas then are injected into the peritoneal cavities of nude mice to produce ascites containing high concentrations (>1 mg/ml) of anti-IGF-1R monoclonal antibody. The resulting monoclonal antibodies may be purified by ammonium sulfate precipitation followed by gel exclusion chromatography, and/or affinity chromatography based on binding of antibody to Protein G.

30   Similar methods can be used to generate human antibodies in transgenic mice. See, e.g., Chen et al., 1993, Internat. Immunol. 5: 647-56; Chen et al., 1993, EMBO J. 12: 821-30; Choi et al., 1993, Nature Genetics 4: 117-23; Fishwild et al., 1996, Nature Biotech. 14: 845-51; Harding et al., 1995, Annals New York Acad. Sci.; Lonberg et al., 1994, Nature 368: 856-59; Lonberg, 1994, Handbook Exper.l Pharmacol. 113: 49-101; Lonberg et al., 1995, Internal Rev. Immunol. 13: 65-93; Morrison, 1994, Nature 368: 812-13;

35   Neuberger, 1996, Nature Biotech. 14: 826; Taylor et al., 1992, Nuc. Acids Res. 20: 6287-95; Taylor et al., 1994, Internat. Immunol. 6: 579-91; Tomizuka et al., 1997, Nature Genetics 16: 133-43; Tomizuka et al., 2000, Proc. Nat. Acad. Sci. USA 97: 722-27; Tuaillon et al., 1993, Proc. Nat. Acad. Sci. USA 90: 3720-24; Tuaillon et al., 1994, J. Immunol. 152: 2912-20; Russel et al., 2000, Infection and Immunity April 2000: 1820-26; Gallo et al., 2000, Eur. J. Immunol. 30: 534-40; Davis et al., 1999, Cancer Metastasis Rev.

40   18:421-25; Green, 1999, J. Immunol. Methods 231:11-23; Jakobovits, 1998, Advanced Drug Delivery Rev.

31:33-42; Green *et al.*, 1998, J. Exp. Med. 188: 483-95; Jakobovits, 1998, Exp. Opin. Invest. Drugs 7: 607-14; Tsuda *et al.*, 1997, Genomics 42: 413-21; Mendez *et al.*, 1997, Nature Genetics 15: 146-56; Jakobovits, 1996, Weir's Handbook of Experimental Immunology, The Integrated Immune System Vol. IV, 194.1-194.7; Mendez *et al.*,1995, Genomics 26: 294-307; Jakobovits, 1994, Current Biol. 4: 761-63; Arbones,

5   1994, Immunity 1: 247-60; Green *et al.*, 1994, Nature Genetics 7: 13-21; Jakobovits *et al.*, 1993, Nature 362: 255-58; Jakobovits *et al.*, 1993,. Proc. Nat. Acad. Sci. USA 90: 2551-55.

EXAMPLE 2: Isolation of Human IGF-1R(ECD)-C3-muIgG1

This example provides a method of making a soluble fragment of IGF-1R useful for raising

10   antibodies.

Cloning of pDSRα:huIGF-1R(ECD)-C3-muIgG1Fc

Primers 2830-36:

5' AGCAAGCTTCCACCATGAAGTCTGGCTCCGGAGGAGG 3' SEQ ID NO:256)
        and 2830-38:

15   5' ATTTGTCGACTTCGTCCAGATGGATGAAGTTTTCAT 3', SEQ ID NO:257)

were used to amplify the human IGF-1R extracellular domain (1-906) cDNA sequence. The primers included a Kozak translation initiation sequence (underlined above) preceding the start codon, restriction sites for subsequent subcloning, and a caspace-3 site, which is inserted next to the extracellular domain C-terminus. PCR was performed on a PerkinElmer 2400 (PerkinElmer, Torrance, CA) under the following

20   conditions: 1 cycle at 95° C for 2 min, 23 cycles at 95° C for 30 sec, 58.5° C for 30 sec, and 72° C for 3 min, and 1 cycle at 72° C for 10 min. Final reaction conditions were 1X *pfu* TURBO® buffer (Stratagene, La Jolla, CA), 200 μM dNTPs, 2 μM each primer, 5 U *pfu* TURBO® (Stratagene) and 1 ng template DNA. The PCR product was purified using a Clontech Nucleospin Column (Clontech, Palo Alto, CA) according to the manufacturers instructions, digested with *Hind* III and *Sal* I (Roche, Indianapolis, IN) and gel

25   purified. The human IGF-1R insert was ligated into *Hind* III/*Sal* I digested pDSRα-muIgG1. Integrity of the insert was confirmed by DNA sequencing. The sequence of the protein encoded by the resulting open reading frame (IGF-1R-C3-muFc) is shown in Figure 10. The final expression vector, pDSRα:huIGF1R(ECD)-C3-muIgG1Fc, is described in Table 1.

Table 1

30   **pDSRα:huIGF1R(ECD)-C3-muIgG1Fc**

Plasmid Base

Pair Number:

11-3496	HuIGF1R (Caspase 3 site)-muIgG1Fc atgaagtctggctccggaggagggtccccgacctcgctgtgggggctcctgtttctctccgccgcgctctcgctctggccga cgagtggagaaatctgcgggccaggcatcgacatccgcaacgactatcagcagctgaagcgcctggagaactgcacggt gatcgagggctacctccacatcctgctcatctccaaggccgaggactaccgcagctaccgcttcccaagctcacggtcatt accgagtacttgctgctgttccgagtggctggcctcgagagcctcggagacctcttcccaacctcacggtcatccgcggct ggaaactcttctacaactacgccctggtcatcttcgagatgaccaatctcaaggatattgggctttacaacctgaggaacattac tcggggggccatcaggattgagaaaaatgctgacctctgttacctctccactgtggactggtccctgatcctggatgcggtgt ccaataactacattgtgggggaataagcccccaaaggaatgtggggacctgtgtccagggaccatggaggagaagccgatg tgtgagaagaccaccatcaacaatgagtacaactaccgctgctggaccacaaaccgctgccagaaaatgtgcccaagcac gtgtgggaagcgggcgtgcaccgagaacaatgagtgctgccaccccgagtgcctgggcagctgcagcgcgcctgacaa

	cgacacggcctgtgtagcttgccgccactactactatgccggtgtctgtgtgcctgcctgcccgcccaacacctacaggtttg agggctggcgctgtgtggaccgtgacttctgcgccaacatcctcagcgccgagagcagcgactccgaggggtttgtgatcc acgacggcgagtgcatgcaggagtgcccctcgggcttcatccgcaacggcagccagagcatgtactgcatcccttgtgaa ggtccttgcccgaaggtctgtgaggaagaaaagaaaacaaagaccattgattctgttacttctgctcagatgctccaaggatg caccatcttcaagggcaatttgctcattaacatccgacgggggaataacattgcttcagagctggagaacttcatggggctcat cgaggtggtgacgggctacgtgaagatccgccattctcatgccttggtctccttgtccttcctaaaaaaccttcgcctcatccta ggagaggagcagctagaagggaattactccttctacgtcctcgacaaccagaacttgcagcaactgtgggactgggaccac cgcaacctgaccatcaaagcagggaaaatgtactttgctttcaatcccaaattatgtgtttccgaaatttaccgcatggaggaa gtgacggggactaaagggcgccaaagcaaaggggacataaacaccaggaacaacggggagagagcctcctgtgaaagt gacgtcctgcatttcacctccaccaccacgtcgaagaatcgcatcatcataacctggcaccggtaccggccccctgactaca gggatctcatcagcttcaccgtttactacaaggaagcaccctttaagaatgtcacagagtatgatgggcaggatgcctgcggc tccaacagctggaacatggtggacgtggacctcccgcccaacaaggacgtggagcccggcatcttactacatgggctgaa gccctggactcagtacgccgtttacgtcaaggctgtgaccctcaccatggtggagaacgaccatatccgtggggccaagag tgagatcttgtacattcgcaccaatgcttcagttccttccattcccttggacgttctttcagcatcgaactcctcttctcagttaatcg tgaagtggaacccctccctctctgcccaacggcaacctgagttactacattgtgcgctggcagcggcagcctcaggacggcta cctttaccggcacaattactgctccaaagacaaaatccccatcaggaagtatgccgacggcaccatcgacattgaggaggtc acagagaaccccaagactgaggtgtgtggtggggagaaagggccttgctgcgcctgccccaaaactgaagccgagaagc aggccgagaaggaggaggctgaataccgcaaagtctttgagaatttcctgcacaactccatcttcgtgcccagacctgaaag gaagcggagagatgtcatgcaagtggccaacaccaccatgtccagccgaagcaggaacaccacggccgcagacacccta caacatcactgacccggaagagctggagacagagtacccctttctttgagagcagagtggataacaaggagagaactgtcatt tctaaccttcggcctttcacattgtaccgcatcgatatccacagctgcaaccacgaggctgagaagctgggctgcagcgcctc caacttcgtctttgcaaggactatgcccgcagaaggagcagatgacattcctgggccagtgacctgggagccaaggcctga aaactccatctttttaaagtggccggaacctgagaatcccaatggattgattctaatgtatgaaataaaatacggatcacaagtt gaggatcagcgagaatgtgtgtccagacaggaatacaggaagtatggagggggccaagctaaaccggctaaacccggggga actacacagcccggattcaggccacatctctctctgggaatgggtcgtggacagatcctgtgttcttctatgtccaggccaaaa caggatatgaaaacttcatccatctggacgaagtcgacggttgtaagccttgcatatgtacagtcccagaagtatcatctgtctt catcttcccccccaaagcccaaggatgtgctcaccattactctgactcctaaggtcacgtgtgttgtggtagacatcagcaagga tgatcccgaggtccagttcagctggtttgtagatgatgtggaggtgcacacagctcagacgcaacccccgggaggagcagtt caacagcactttccgctcagtcagtgaacttcccatcatgcaccaggactggctcaatggcaaggagttcaaatgcagggta aacagtgcagctttccctgcccccatcgagaaaaccatctccaaaaccaaaggcagaccgaaggctccacaggtgtacacc attccacctcccaaggagcagatggccaaggataaagtcagtctgacctgcatgataacagacttcttccctgaagacattac tgtggagtggcagtggaatgggcagccagcggagaactacaagaacactcagcccatcatggacacagatggctcttactt cgtctacagcaagctcaatgtgcagaagagcaactgggaggcaggaaatactttcacctgctctgtgttacatgagggcctg cacaaccaccatactgagaagagcctctcccactctcctggtaaa (SEQ ID NO:258)
3507 to 4391	A transcription termination/polyadenylation signal from the α-subunit of the bovine pituitary glycoprotein hormone (α-FSH) (Goodwin et al., 1983, Nucleic Acids Res. 11:6873-82; Genbank Accession Number X00004)
4600 to 5163	A mouse dihydrofolate reductase (DHFR) minigene containing the endogenous mouse DHFR promoter, the cDNA coding sequences, and the DHFR transcription termination/polyadenylation signals (Gasser et al., 1982, Proc. Natl. Acad. Sci. U. S. A. 79:6522-6; Nunberg et al., 1980, Cell 19:355-64; Setzer et al., 1982, J. Biol. Chem. 257:5143-7; McGrogan et al., 1985, J. Biol. Chem. 260:2307-14)
6389 to 7246	pBR322 sequences containing the ampicillin resistance marker gene and the origin for replication of the plasmid in E. coli (Genbank Accession Number J01749)
7459 to 7802	An SV40 early promoter, enhancer and origin of replication (Takebe et al., 1988, Mol. Cell Biol. 8:466-72, Genbank Accession Number J02400)
7809 to 8065	A translational enhancer element from the HTLV-1 LTR domain (Seiki et al., 1983, Proc. Natl. Acad. Sci. U. S. A. 80:3618-22, Genbank Accession Number J02029)
8109 to 8205	An intron from the SV40 16S, 19S splice donor/acceptor signals (Okayama and Berg, 1983. Mol. Cell Biol. 3:280-9, Genbank Accession Number J02400)

Expression of hu IGF-1R(ECD)-C3-muIgG1Fc

Fifteen micrograms of linearized expression vector pDSRα:huIGF1R(ECD)-C3-muIgG1Fc was transfected into AM-1/D CHOd- cells using LT1 lipofection reagent (PanVera Corp., Madison, WI), and cells cultured under conditions to allow expression and secretion of protein into the cell media. Twenty-four colonies were selected after 10-14 days on DHFR selection medium (Dulbecco's Modified Eagles

Medium (Invitrogen) supplemented with 10% dialyzed fetal bovine serum, 1x penicillin-streptomycin (Invitrogen)) and expression levels evaluated by western blot. To perform this assay, 0.5 ml of serum free medium was added to a single well confluent cells cultured in a 24 well plate (Falcon). The conditioned medium was recovered after 48hr. Samples for western blotting were run in 10% Tris-glycine gel (Novex),

5 and blotted on 0.45 μm Nitrocellulose membrane (Invitrogen), using the Mini Trans-Blot cell (Biorad). The blotted membranes were incubated with rabbit anti-mouse IgG Fc antibody, conjugated with Horseradish Peroxidase (Pierce). The clone expressing the highest level of IGF-1R(ECD)-C3-muIgG1Fc was expanded in DHFR selection medium and 2×10^7 cells were inoculated into 50 roller bottles each (Corning) in 250 ml of high-glucose DMEM (Invitrogen), 10% dialyzed FBS (Invitrogen), 1x glutamine (Invitrogen), 1x Non

10 essential amino acids (Invitrogen), 1x sodium pyruvate (Invitrogen). Medium was gassed with 10% CO_2/balance air for 5 seconds before capping the roller bottle. Roller bottles were kept at 37° C on roller racks spinning at 0.75 rpm.

When cells reached approximately 85-90% confluency (after approximately 5-6 days in culture), growth medium was discarded, cells washed with 100 ml PBS and 200 ml production medium was added

15 (50 % DMEM (Invitrogen)/ 50 % F12 (Invitrogen), 1x glutamine (Invitrogen), 1x non-essential amino acids (Invitrogen), 1x sodium pyruvate (Invitrogen), 1.5% DMSO (Sigma)). The conditioned medium was harvested and replaced at one week intervals. The resulting 30 liters of conditioned medium were filtered through a 0.45 μm cellulose acetate filter (Corning, Acton, MA).

20 <u>Purification of hu IGF-1R(ECD)-C3-muIgG1Fc</u>

The resulting filtrate from the conditioned medium was concentrated 20-fold using a spiral-wound cartridge (molecular weight cut-off = 10 kDa), then diluted 1:1 with 3 M KCl, 1 M glycine, pH 9.0 to bring the final salt concentration to 1.5 M KCl, 0.5 M glycine, pH 9.0. This sample was applied to a rProtein A-Sepharose column (Amersham Pharmacia Biotech, Uppsala, Sweden) which had been equilibrated in 1.5 M

25 KCl, 0.5 M glycine, pH 9.0. The column was washed with 40 column volumes of the same buffer, then eluted with 20 column volumes of 0.1 M glycine-HCl, pH 2.8. Five-mL fractions were collected and immediately neutralized with 1 mL of 1 M Tris-HCl, pH 7.5. Fractions containing huIGF1R(ECD)-C3-muIgGFc were identified by SDS-PAGE, pooled, and dialyzed against phosphate-buffered saline. The yield was 2.4 mg/L of conditioned medium. The major protein species detected were the mature α and β

30 chains and murine Fc, each of which appeared to be properly glycosylated based on their elevated and heterogeneous molecular weights. Unprocessed IGF-1R(ECD), as well as glycosylated but not proteolytically cleaved IGF-1R(CED), was also present in the preparation. The shift in bands to higher molecular weights under non-reducing conditions indicates that disulfide linkages joined the α and β chains. Amino-terminal sequencing of the final product indicated that 60% of the protein was correctly processed

35 between the α- and β-chains of IGF-1R(ECD), while 40% remained unprocessed.

EXAMPLE 3: Isolation of Human INSR(ECD)-muIgG1

This example presents a method of cloning and expressing a soluble fragment of the human insulin receptor.

40 Cloning of pDSRα:huINSR(ECD)-muIgG1Fc

Primers 2830-40:

5' AGC<u>AAGCTT</u>CCACCATGGGCACCGGGGGCCGG 3' SEQ ID NO:259

(Hind III site underlined) and 2830-41:

5' ATTT<u>GTCGAC</u>TTTTGCAATATTTGACGGGACGTCTAA 3' SEQ ID NO:260

5   (Sal I site underlined) were used to amplify the human INSR extracellular domain (1-929) from and INSR parental plamid encoding the B form of the INSR splice variant (Ullrich et al., 1985, Nature 313:756-61; Ebina et al., 1985, Cell 40:747-58). The primers included a Kozak translation initiation sequence preceding the start codon and restriction sites for subsequent sub-cloning. PCR was performed on a PerkinElmer 2400 under the following conditions: 1 cycle at 95° C for 2 min, 32 cycles at 95° C for 30 sec, 58.5° C for 30

10   sec, and 72° C for 3 min, and 1 cycle at 72° C for 10 min. Final reaction conditions were 1X pfu TURBO® buffer, 200 µM dNTPs, 2 µM each primer, 5 U pfu TURBO® (Stratagene) and 10 ng template DNA. The PCR product was purified using a NUCLEOSPIN® Column (BD Biosciences Clontech, Palo Alto, CA) according to the manufacturer's instructions, digested with Hind III and Sal I (Roche), and gel purified prior to ligation into Hind III/Sal I digested pDSRα-muIgG1. The integrity of the insert was confirmed by DNA

15   sequencing. The protein sequence of the INSR-muFc is shown in Figure 11. The final expression vector is described in Table 2.

Table 2

<u>Plasmid Base</u>

20   <u>Pair Number:</u>

11-3550	HuINSR-muIgG1Fc
	atgggcaccggggggccggcggggggcggcggccgcgccgctgctggtggcggtggccgcgctgctactgggcgccg cggcgccacctgtaccccggagaggtgtgtcccggcatggatatccggaacaacctcactaggttgcatgagctggagaatt gctctgtcatcgaaggacacttgcagatactcttgatgttcaaaacgaggccccgaagatttccgagacctcagtttccccaaac tcatcatgatcactgattacttgctgctcttccgggtctatgggctcgagagcctgaaggacctgttccccaacctcacggtcat ccgggggatcacgactgttctttaactacgcgctggtcatcttcgagatggttcacctcaaggaactcggcctctacaacctgat gaacatcacccgggggttctgtccgcatcgagaagaacaatgagctctgttacttggccactatcgactggtcccgtatcctgg attccgtggaggataatcacatcgtgttgaacaaagatgacaacgaggagtgtggagacatctgtccgggtaccgcgaagg gcaagaccaactgccccgccaccgtcatcaacgggcagtttgtcgaacgatgttggactcatagtcactgccagaaagtttg cccgaccatctgtaagtcacacggctgcaccgccgaaggcctctgttgccacagcgagtgcctgggcaactgttctcagcc cgacgaccccaccaagtgcgtggcctgccgcaacttctacctggacggcaggtgtgtggagacctgcccgcccccgtact. accacttccaggactggcgctgtgtgaacttcagcttctgccaggacctgcaccacaaatgcaagaactcgcggaggcagg gctgccaccagtacgtcattcacaacaacaagtgcatccctgagtgtccctccgggtacacgatgaattccagcaacttgctg tgcaccccatgcctgggtccctgtcccaaggtgtgccacctcctagaaggcgagaagaccatcgactcggtgacgtctgcc caggagctccgaggatgcaccgtcatcaacgggagtctgatcatcaacattcgaggaggcaacaatctggcagctgagcta gaagccaacctcggcctcattgaagaaatttcagggtatctaaaaatccgccgatcctacgctctggtgtcactttccttcttcc ggaagttacgtctgattcgaggagagagaccttggaaattgggaactactccttctatgccttggacaaccagaacctaaggcag ctctgggactggagcaaacacaacctcaccaccactcaggggaaactcttcttccactataaccccaaactctgcttgtcaga aatccacaagatggaagaagtttcaggaaccaaggggcgccaggagagaaacgacattgccctgaagaccaatggggac aaggcatcctgtgaaaatgagttacttaaatttttcttacattcggacatcttttgacaagatcttgctgagatgggagccgtactg gcccccccgacttccgagacctcttgggggttcatgctgttctacaaagaggcccccttatcagaatgtgacggagttcgatgggc aggatgcgtgtggttccaacagttggacggtggtagacattgacccacccctgaggtccaacgaccccaaatcacagaacc acccagggtggctgatgcgggggtctcaagccctggacccagtatgccatctttgtgaagaccctggtcaccttttcggatgaa cgccggacctatggggccaagagtgacatcatttatgtccagacagatgccaccaaccccctctgtgcccctggatccaatct cagtgtctaactcatcatcccagattattctgaagtggaaaccaccctccgaccccaatggcaacatcacccactacctggtttt ctgggagaggcaggcggaagacagtgagctgttcgagctggattattgcctcaaagggctgaagctgccctcgaggacct ggtctccaccattcgagtctgaagattctcagaagcacaaccagagtgagtatgaggattcggccggcgaatgctgctcctgt ccaaagacagactctcagatcctgaaggagctggaggagtcctcgtttaggaagacgtttgaggattacctgcacaacgtgg ttttcgtccccagaaaaaacctcttcaggcactggtgccgaggacccctaggccatctcggaaacgcaggtcccttggcgatgtt

	gggaatgtgacggtggccgtgcccacggtggcagctttccccaacacttcctcgaccagcgtgcccacgagtccggagga gcacaggccttttgagaaggtggtgaacaaggagtcgctggtcatctccggcttgcgacacttcacgggctatcgcatcgag ctgcaggcttgcaaccaggacacccctgaggaacggtgcagtgtggcagcctacgtcagtgcgaggaccatgcctgaagc caaggctgatgacattgttggccctgtgacgcatgaaatctttgagaacaacgtcgtccacttgatgtggcaggagccgaag gagcccaatggtctgatcgtgctgtatgaagtgagttatcggcgatatggtgatgaggagctgcatctctgcgtctcccgcaa gcacttcgctctggaacggggctgcaggctgcgtgggctgtcaccggggaactacagcgtgcgaatccgggccacctccc ttgcgggcaacggctcttggacggaacccacctatttctacgtgacagactatttagacgtcccgtcaaatattgcaaaagtcg acggttgtaagccttgcatatgtacagtcccagaagtatcatctgtcttcatcttcccccccaaagcccaaggatgtgctcaccat tactctgactcctaaggtcacgtgtgttgtggtagacatcagcaaggatgatcccgaggtccagttcagctggtttgtagatgat gtggaggtgcacacagctcagacgcaaccccgggaggagcagttcaacagcactttccgctcagtcagtgaacttcccatc atgcaccaggactggctcaatggcaaggagttcaaatgcagggtaaacagtgcagctttccctgcccccatcgagaaaacc atctccaaaaccaaaggcagaccgaaggctccacaggtgtacaccattccacctcccaaggagcagatggccaaggataa agtcagtctgacctgcatgataacagacttcttccctgaagacattactgtggagtggcagtggaatgggcagccagcggag aactacaagaacactcagcccatcatggacacagatggctcttacttcgtctacagcaagctcaatgtgcagaagagcaact gggaggcaggaaatactttcacctgctctgtgttacatgagggcctgcacaaccaccatactgagaagagcctctcccactct cctggtaaa (SEQ ID NO:261)
3557 to 4441	A transcription termination/polyadenylation signal from the α-subunit of the bovine pituitary glycoprotein hormone (α-FSH) (Goodwin *et al.*, 1983, *Nucleic Acids Res.* 11:6873-82; Genbank Accession Number X00004)
4446 to 5586	A mouse dihydrofolate reductase (DHFR) minigene containing the endogenous mouse DHFR promoter, the cDNA coding sequences, and the DHFR transcription termination/polyadenylation signals (Gasser *et al.*, 1982, *Proc. Natl. Acad. Sci. U. S. A.* 79:6522-6; Nunberg *et al.*, 1980, *Cell* 19:355-64; Setzer *et al.*, 1982, *J. Biol. Chem.* 257:5143-7; McGrogan *et al.*, 1985, *J. Biol. Chem.* 260:2307-14)
5594 to 6241	pBR322 sequences containing the ampicillin resistance marker gene and the origin for replication of the plasmid in *E. coli* (Genbank Accession Number J01749)
7513 to 7856	An SV40 early promoter, enhancer and origin of replication (*Takebe et al.*, 1988, *Mol. Cell Biol.* 8:466-72, Genbank Accession Number J02400)
7863 to 8119	A translational enhancer element from the HTLV-1 LTR domain (Seiki *et al.*, 1983, *Proc. Natl. Acad. Sci. U. S. A.* 80:3618-22, Genbank Accession Number J02029)
8163 to 8259	An intron from the SV40 16S, 19S splice donor/acceptor signals (Okayama and Berg, 1983. *Mol. Cell Biol.* 3:280-9, Genbank Accession Number J02400)

Expression of hu INSR(ECD)-C3-muIgG1Fc

AM-1/D CHOd- cells were transfected with 15 μm of linearized expression vector pDSRa:huINSR(ECD) –muIgG1Fc using FUGENE™ 6 lipofection reagent (Roche Diagnostics Corp., Indianapolis, IN), then cultured under conditions to allow expression and secretion of protein into the cell medium. Colonies were selected and analyzed as described above.

Purification of hu INSR(ECD)-C3-muIgG1Fc

The filtered conditioned medium containing huINSR(ECD)-muIgGFc was concentrated 17-fold using a spiral-wound cartridge (molecular weight cut-off = 10 kDa), then diluted 1:1 with 3 M KCl, 1 M glycine, pH 9.0 to bring the final salt concentration to 1.5 M KCl, 0.5 M glycine, pH 9.0. This sample was applied to a rProtein A-Sepharose column (Pharmacia) which had been equilibrated in 1.5 M KCl, 0.5 M glycine, pH 9.0. The column was washed with 40 column volumes of the same buffer, then eluted with 20 column volumes of 0.1 M glycine-HCl, pH 2.8. Five-mL fractions were collected and immediately neutralized with 1-mL of 1 M Tris-HCl, pH 7.5. Fractions containing huINSR(ECD)-muIgGFc were identified by SDS-PAGE, pooled, and dialyzed against phosphate-buffered saline. The yield was 0.9 mg/L of conditioned medium. The major protein species were the mature α and β chains and murine Fc. Each of these species appeared to be properly glycosylated based on its elevated and heterogeneous molecular

weight. Unprocessed INSR (ECD) as well as glycosylated but not proteolytically cleaved INSR (CED) also was present in the preparation. The shift in bands to higher molecular weights under non-reducing conditions indicated that disulfide linkages joined the α and β chains. Amino-terminal sequencing of the final product indicated that 87% of the protein was correctly processed between the α- and β-chains of

5   INSR(ECD), while 13% remained unprocessed.

EXAMPLE 3: Initial Screen for Anti-IGF-1R phage Fab

This example provides a method of identifying anti-IGF-1R antibodies.

A Target Quest Q Fab library ("the TQ library"; Target Quest, Maastricht, the Netherlands), which

10   was constructed using peripheral blood lymphocytes from four healthy donors and splenic lymphocytes from one patient with gastric carcinoma, was obtained. The library diversity was 3.7×10^{10} clones, containing 3×10^9 heavy chains. The source, screening methods, and characterization of the library have been published (de Haard *et al*, 1999, J Biol Chem 274:18218-30). Dynabeads (200 μl) M-450 Uncoated (catalog # 140.02, Dynal, Lake Success, NY) were washed 3 times with PBS, resuspended in 200 μl of

15   IGF1R(ECD)-C3-mFc to a concentration of 0.5 μM in PBS, and incubated at 4° C on a rotator overnight. The IGF-1R(ECD)-C3-mFc coated beads were washed 3x with 1 ml of 2% non-fat dry milk (M) in PBS (2% MPBS), and then blocked with 1 ml of 2% MPBS at room temperature for 1 hour. In parallel, 750 μl of the TQ library (4×10^{12} pfu) was preblocked by mixing with 250 μl 8% MPBS at room temperature for 30 minutes to 1 hour. 500 μl of blocked beads were transferred into another microfuge tube and separated

20   from the blocking solution on a magnetic separator. The preblocked phage mixture was added to the blocked beads and incubated for 90 minutes on a rotator at room temperature. Bead-bound phage were separated from the unbound phage, and then washed 6x with 1ml 2% MPBS/0.1% Tween 20, 6x with 1ml PBS/0.1% Tween 20, 2x with PBS with a change of tubes between different wash solutions. Bound phage was eluted with 1 ml of 0.1M TEA (pH11) for 10 minutes, then immediately separated from the beads and

25   neutralized with 0.5 ml of 1 M Tris.HCl. The eluted phage pool was mixed with 4 ml 2x YT broth (10 g yeast extract, 16 g bacto-tryptone, 5 g NaCl per liter of water) and 5 ml of TG1 bacterial culture (O.D. $_{590}$ about 0.5) in a 50-ml conical tube. The infection mixture was incubate at 37° C in an incubator for 30 min., then centrifuged at 3500 rpm for 20 min. The cell pellet was resuspended in 1500 μl 2xYT-CG broth and 300 μl were spread on each of five 2xYT-CG (2x YT broth containing 100 μg/ml carbenicillin and 2%

30   glucose) plates. After 20 hours of incubation at 30° C, 4 ml of 2x YT-AG were added to each plate and the cells were recovered with cell scraper from the plates. This step was repeated three times. A small portion of the recovered cells was used for phage rescue (see below). The remaining cell suspension was centrifuged at 3500 rpm for 20 min. The cell pellet was suspended into an amount of 50% glycerol roughly half the volume of the pellet size and stored at –80° C.

35   In order to rescue phage, the plated-amplified cell suspension was used to inoculate 40 ml of 2x YT-CG to an OD$_{590}$ of about 0.05. The culture was incubated at 37° C on a shaker to OD$_{590}$ 0.5. The log phase culture was infected with M13KO7 helper phage (GIBCO BRL, Gaithersburg, MD, catalog # 18311-019, 1.1×10^{11} pfu/ml) at M.O.I. 20 followed by incubation at 37° C for 30 min. The infected cells were centrifuged at 4000 rpm for 20 min. The cell pellet was re-suspended in 200 ml of 2xYT-CK (100 μg/ml

carbenicillin and 40 µg/ml kanamycin) and transferred to two 250-ml flasks and incubated at 30° C with shaking at 270 rpm for 20 hours. The over-night culture was centrifuged at 4000 rpm for 20 min to removal cell debris. The centrifugation was repeated to ensure the removal of cell debris. About 1/5 volume of PEG solution (20% PEG 8000, 2.5 M NaCl) was added to the supernatant to precipitate the phage particles.

5   The mixture was incubated on ice for at least 1 hour, followed by centrifugation at 4000 rpm for 20 min to collect the precipitated phage particles. The phage pellet was re-suspended into 1 ml of PBS and transferred to a microfuge tube. The phage suspension was left on ice for 1 hour to allow complete suspension of phage particles, and clarified by centrifugation at 14,000 rpm for 2 min to remove the residual cell debris. Phage precipitation step was repeated. The final phage pellet was suspended into PBS

10   after clarification. The rescued phage suspension was used in the next round of selection.

        Four rounds of selection were performed that included alterations of various standard binding parameters. The second round of selection was identical to the first round of selection. Variations in input phage number and elution reagent were introduced in rounds three and four. For the round three selection, $5x10^{11}$ pfu of phages were selected and bound phages were eluted either with 1 µM IGF-1 (catalog # I3769,

15   Sigma, St. Louis, MO) or with a 1 µM concentration of a chimeric αIR3-huFc antibody to yield two round-three pools, TQ4-3IS and TQ4-3CA. Round four selection was carried out on rescued phage pools from both round three pools. Two rounds of negative selection with mouse IgG Fc-coated DYNABEADS® (Dynal Biotech, Oslo, Norway) were included to remove mouse Fc binders prior to actual IGF-1R selection. The incubation time for negative selection was 30 minutes each. $3.78x10^{11}$ pfu of TQ4-3IS pool and

20      $3.75x10^{12}$ pfu of TQ4-3CA pool were selected separately. Bound phage were eluted with 1 µM IGF-2 (catalog # I2526, Sigma, St. Louis, MO) to yield two round-4 pools, TQ4-4ISI2 and TQ4-4CAI2. The sequence of about 96-192 phage DNA inserts was determined at each elution step.

        In some cases, a secondary screen was done. Phagemid DNA mixtures of the total TQ library, and the selected phage amplified after several rounds of selection against IGF-1R, were prepared using a DNA

25   Maxiprep kit according to the manufacturer's instructions (Qiagen, Valencia, CA). All four DNA preparations were digested with *Asc* I and *Eco*R I (New England Biolab, Beverly, MA). The resulting two *Asc* I/*Eco*R I fragments were separated on preparative 0.5% agarose gels. The 2.1 kb fragments containing heavy chains were gel purified from the IGF-1R selected phage. The 3.9 kb fragments containing the light chains and pCES1 vector portion were gel purified from the total TQ library DNA. The 2.1 kb fragments

30   were ligated to the 3.9 kb fragments from the DNA sample of TQ library in 3:1 ratio. The ligated DNA was precipitated and used to transform TG1 cells by electroporation. The library size of the resulted light chain shuffled secondary library was $8.8x10^8$. After sequencing 96 randomly picked clones, 76 unique light chain sequences were obtained, indicating that the attempt to shuffle light chains was successful.

        The binding, washing and elution condition for screening the light chain shuffle library were

35   essentially the same as decribed for the intial screen. However, several variations were included to increase selection pressure for amplification of IGF-1R binders with higher affinities, especially those with significantly slower off-rates. These parameters were: higher number of input phage (2-2.7 x10^{13} pfu), smaller bead volume (100 µl for round one, 50 µl for round two, and 25 µl for round three), and extended specific elution time up to 20 hours. Elution buffers were 0.1 M TEA for round one (RD1), 1 µM IGF-1 in

40   0.4% MPBS for RD2 and 1 µM IGF-1 or IGF-2 in 0.4% MPBS for RD3. In RD2 and RD3, binders that

were eluted in 15 min or 2 hours were discarded. Elution was continued and eluted phages were collected after 8-10 hours and again after 20 hours.

Phage Fab ELISA Screen

5   In 96-well 2-ml deep-well blocks, 480 μl/well 2xYT-CG broth was inoculated with 20 μl of overnight cultures of the individual clones, then incubated at 37° C, 300 rpm for 3 hours. To each well, 50 μl of 1:3 diluted M13KO7 helper phage were added to infect the cells. The block was incubated at 37° C without shaking for 30 minutes, and then shaken gently for another 30 minutes at 150 rpm. The block was centrifuged at 3600 rpm for 20 minutes to pellet the infected cells. The cell pellet in each well was

10   suspended into 480 μl of 2xYT-CK (2xYT broth containing 100 μg/ml carbenicillin and 40 μg/ml kanamycin), and incubated at 30° C overnight for about 20 hours. The cell debris was separated by centrifugation at 3600 rpm for 20 minutes. The rescued phage supernatant was used in the phage ELISA to check for IGF-1R-specific, INSR-cross reactive, or mouse Fc binding of individual clones.

         Three sets of Nunc MaxiSorb Immunoplates were coated with 100 μl/well of IGF-1R-C3-mFc at 5

15   μg/ml, INSR-mFc at 5 μg/ml, or mouse IgG1 (catalog # 010-0103, Rockland, Gilbertsville, PA) at 2 μg/ml in PBS, respectively, at 4° C overnight. The coated plates were washed 3x with 300 μl/well of PBS. The washed plates were blocked with 300 μl/well 2% MPBS at room temperature for one hour. Meanwhile, rescued phages of individual clones were pre-blocked by mixing 170 μl of rescued phage with 170 μl of 4% MPBS. The blocked plates were washed 5x with 300 μl/well TBST (TBS: 10 mM Tris-HCl, pH 7.5, 1 mM

20   EDTA, 150 mM NaCl; Tween-20. 0.1%). 100 μl/well of pre-blocked phage dilutions were distributed to each set of coated plate, which were incubated at room temperature on a rocker for 90 minutes. The plates were washed 5x with 300 μl/well TBST. 100 μl/well of anti-M13-HRP in 2% MPBS (1:3000 dilution, catalog number 27-9421-01, Amersham Pharmacia Biotech) were distributed, and plates were incubated at room temperature on rocker for one hour. The plates were washed 5x with 300 μl/well TBST. 100 μl/well

25   of the substrate 1-Step™ ABTS (Pierce Biotechnology, Rockford, IL, catalog number 37615) were added. Plates were incubated for one hour. OD_{405} was measured for signal detection.

         The phage displayed antibodies exhibited essentially no crossreactivity with the insulin receptor and murine Fc domain. The signal observed in the IGF-1R ELISA is therefore specific for the IGF-1R extracellular domain. Results from similar assays for four of the phage-displayed antibodies are shown in

30   Figure 14.

         The DNA inserts of IGF-1R positive, INSR and mu IgG1 negative, clones were sequenced. Fifty-two unique Fab sequences were identified, having the following combinations of light chain and heavy chain variable domain sequences: L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20, H20, L21H21,

35   L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52, wherein "Lx" indicates light chain variable domain number "x" and "Hx" indicates heavy chain variable domain number

"x." Figure 1 presents the polynucleotide sequences of each of these light and heavy variable domains. Figures 2 and 3 present the corresponding amino acid sequences.

EXAMPLE 4: Subcloning of V_H and V_L into IgG1 expression vectors

5   This example presents a method of subcloning the previously identified variable domain sequences into an IgG1 expression vector.

Construction of pDSRα20 and pDSRα20:hIgG1C$_H$

          The pDSRα20:hIgG1C$_H$ expression vector (WO 90/14363) was a derivative of pDSR19:hIgG1C$_H$

10   (see U.S. Provisional Patent Application No. 60/370,407, filed April 5, 2002, "Human Anti-OPGL Neutralizing Antibodies As Selective OPGL Pathway Inhibitors," incorporated herein by reference in its entirety). The pDSRα19:hIgG1C$_H$ plasmid encoded a rat variable region/human constant region IgG1 (rVh/hCh1). The plasmid was constructed by the three-piece ligation of Xba I and BsmB I terminated rat antibody variable region PCR product, the human IgG1 constant region (C$_{H1}$, hinge, C$_{H2}$ and C$_{H3}$ domains)

15   derived by Sal I cleavage and gel isolation of the BsmB I and Sal I fragment from the linear plasmid pDSRα19:hIgG1 C$_H$ (Hind III and BsmB I ends) and a linearized pDSRα19 with Xba I and Sal I ends. pDSRα20 was produced by changing nucleotide 2563 in pDSRα19 from a guanosine to an adenosine by site directed mutagenesis. The heavy chain expression vector, pDSRα20:hIgG1C$_H$ rat variable region/human constant region IgG1 (rVh/hCh1), is 6163 base pairs and contains the 7 functional regions

20   described in Table 3.

Table 3

Plasmid Base

 Pair Number:

25

2 to 881	A transcription termination/polyadenylation signal from the α-subunit of the bovine pituitary glycoprotein hormone (α-FSH) (Goodwin et al., 1983, Nucleic Acids Res. 11:6873-82; Genbank Accession Number X00004)
882 to 2027	A mouse dihydrofolate reductase (DHFR) minigene containing the endogenous mouse DHFR promoter, the cDNA coding sequences, and the DHFR transcription termination/polyadenylation signals (Gasser et al., 1982, Proc. Natl. Acad. Sci. U. S. A. 79:6522-6; Nunberg et al., 1980, Cell 19:355-64; Setzer et al., 1982, J. Biol. Chem. 257:5143-7; McGrogan et al., 1985, J. Biol. Chem. 260:2307-14)
2031 to 3947	pBR322 sequences containing the ampicillin resistance marker gene and the origin for replication of the plasmid in E. coli (Genbank Accession Number J01749)
3949 to 4292	An SV40 early promoter, enhancer and origin of replication (Takebe et al., 1988, Mol. Cell Biol. 8:466-72, Genbank Accession Number J02400)
4299 to 4565	A translational enhancer element from the HTLV-1 LTR domain (Seiki et al., 1983, Proc. Natl. Acad. Sci. U. S. A. 80:3618-22, Genbank Accession Number J02029)
4574 to 4730	An intron from the SV40 16S, 19S splice donor/acceptor signals (Okayama and Berg, 1983. Mol. Cell Biol. 3:280-9, Genbank Accession Number J02400)

4755 to 6158	The rVh/hCh1 heavy chain cDNA between the Xbal and Sall sites. This heavy chain fragment sequence is shown below (SEQ ID NO: 262) with the sequences of the restriction sites underlined:
	                XbaI
	          TCTAG ACCACCATGG ACATCAGGCT CAGCTTAGTT TTCCTTGTCC

TTTTCATAAA AGGTGTCCAG TGTGAGGTAG AACTGGTGGA
GTCTGGGGGC GGCTTAGTAC AACCTGGAAG GTCCATGACA
CTCTCCTGTG CAGCCTCGGG ATTCACTTTC AGAACCTATG GCATGGCCTG
GGTCCGCCAG GCCCCAACGA AGGGTCTGGA GTGGGTCTCA
TCAATTACTG CTAGTGGTGG TACCACCTAC TATCGAGACT CCGTGAAGGG
CCGCTTCACT ATTTTTAGGG ATAATGCAAA AAGTACCCTA TACCTGCAGA
TGGACAGTCC GAGGTCTGAG GACACGGCCA CTTATTTCTG TACATCAATT
TCGGAATACT GGGGCCACGG AGTCATGGTC
*BsmB*1
ACC<u>CGTCTC</u>TA GTGCCTCCAC CAAGGGCCCA TCGGTCTTCC CCCTGGCACC
CTCCTCCAAG AGCACCTCTG GGGGCACAGC GGCCCTGGGC
TGCCTGGTCA AGGACTACTT CCCCGAACCG GTGACGGTGT
CGTGGAACTC AGGCGCCCTG ACCAGCGGCG TGCACACCTT
CCCGGCTGTC CTACAGTCCT CAGGACTCTA CTCCCTCAGC AGCGTGGTGA
CCGTGCCCTC CAGCAGCTTG GGCACCCAGA CCTACATCTG
CAACGTGAAT CACAAGCCCA GCAACACCAA GGTGGACAAG
AAAGTTGAGC CCAAATCTTG TGACAAAACT CACACATGCC
CACCGTGCCC AGCACCTGAA CTCCTGGGGG GACCGTCAGT CTTCCTCTTC
CCCCCAAAAC CCAAGGACAC CCTCATGATC TCCCGGACCC
CTGAGGTCAC ATGCGTGGTG GTGGACGTGA GCCACGAAGA
CCCTGAGGTC AAGTTCAACT GGTACGTGGA CGGCGTGGAG
GTGCATAATG CCAAGACAAA GCCGCGGGAG GAGCAGTACA
ACAGCACGTA CCGTGTGGTC AGCGTCCTCA CCGTCCTGCA
CCAGGACTGG CTGAATGGCA AGGAGTACAA GTGCAAGGTC
TCCAACAAAG CCCTCCCAGC CCCCATCGAG AAAACCATCT
CCAAAGCCAA AGGGCAGCCC CGAGAACCAC AGGTGTACAC
CCTGCCCCCA TCCCGGGATG AGCTGACCAA GAACCAGGTC
AGCCTGACCT GCCTGGTCAA AGGCTTCTAT CCCAGCGACA
TCGCCGTGGA GTGGGAGAGC AATGGGCAGC CGGAGAACAA
CTACAAGACC ACGCCTCCCG TGCTGGACTC CGACGGCTCC TTCTTCCTCT
ATAGCAAGCT CACCGTGGAC AAGAGCAGGT GGCAGCAGGG
GAACGTCTTC TCATGCTCCG TGATGCATGA GGCTCTGCAC AACCACTACA
CGCAGAAGAG CCTCTCCCTG TCTCCGGGTA
*Sal*I
AATGATAA<u>GT CGAC</u>

The linear plasmid pDSRα20:hIgG1C_H was prepared by digesting the pDSR20: rat variable region/human constant region IgG1 plasmid with the restriction enzymes *Xba* I and *Bsm*B I to remove the rat variable region and purified using a QIAquick Gel Extraction kit. The linear plasmid

5   pDSRα20:hIgG1C_H containing the 1.0 kbp human IgG1 constant region domain was used to accept anti-IGF-1R variable heavy chain coding sequences.

<u>Construction of the anti-IGF-1R IgG1 Heavy Chain Expression Clones</u>

The sequence coding for the anti-IGF-1R variable region of the heavy chains was amplified from

10   phagemid DNA with complementary oligonucleotide primers. Primers for polymerase chain reaction (PCR) were designed to incorporate a *Hind* III site, *Xba* I site, Kozak sequence (CCACC) and signal sequence (translated peptide is MDMRVPAQLLGLLLLWLRGARC; SEQ ID NO:263) onto the 5' end of the variable region, while a *Bsm*B I site was added onto the 3' end of the PCR product. The PCR products were digested with *Xba* I and *Bsm*B I, and then cloned into the *Xba* I-*Bsm*B I linear pDSRα20:hIgG1C_H

15   expression vector containing the human IgG1 constant region (Figure 13). The final expression vectors contained the seven functional regions described in Table 4.

65

Table 4

<u>Plasmid Base</u>

<u>Pair Number:</u>

2 to 881	A transcription termination/polyadenylation signal from the α-subunit of the bovine pituitary glycoprotein hormone (α-FSH) (Goodwin *et al.*, 1983, *Nucleic Acids Res.* <u>11</u>:6873-82; Genbank Accession Number X00004)
882 to 2027	A mouse dihydrofolate reductase (DHFR) minigene containing the endogenous mouse DHFR promoter, the cDNA coding sequences, and the DHFR transcription termination/polyadenylation signals (Gasser *et al.*, 1982, *Proc. Natl. Acad. Sci. U. S. A.* <u>79</u>:6522-6; Nunberg *et al.*, 1980, *Cell* <u>19</u>:355-64; Setzer *et al.*, 1982, *J. Biol. Chem.* <u>257</u>:5143-7; McGrogan <u>et al.</u>, 1985, *J. Biol. Chem.* <u>260</u>:2307-14)
2031 to 3947	pBR322 sequences containing the ampicillin resistance marker gene and the origin for replication of the plasmid in *E. coli* (Genbank Accession Number J01749)
3949 to 4292	An SV40 early promoter, enhancer and origin of replication (Takebe *et al.*, 1988, *Mol. Cell Biol.* <u>8</u>:466-72, Genbank Accession Number J02400)
4299 to 4565	A translational enhancer element from the HTLV-1 LTR domain (Seiki *et al.*, 1983, *Proc. Natl. Acad. Sci. U. S. A.* <u>80</u>:3618-22, Genbank Accession Number J02029)
4574 to 4730	An intron from the SV40 16S, 19S splice donor/acceptor signals (Okayama and Berg, 1983. *Mol. Cell Biol.* <u>3</u>:280-9, Genbank Accession Number J02400)
4755 to 6185	The heavy chain IgG1 cDNA between the *Xbal* and *Sall* sites

5

<u>Construction of the anti-IGF-1R IgG1 Variable Chain Expression Clones.</u>

The light chains encoded in anti-IGF-1R phage were either kappa or lambda class. They were cloned using one of two approaches. Complementary primers were designed to add a *Hin*d III site, an *Xba* I site, Kozak sequence (CCACC) and signal sequence (translated peptide is

10   MDMRVPAQLLGLLLLWLRGARC, SEQ ID NO:264) were added to the 5' end of the coding region. Those chains that had error-free coding regions were cloned as full-length products. The full-length light chains were cloned as *Xba* I and *Sal* I fragments into the expression vector pDSRα20. The final expression vectors contained the seven functional regions described in Table 5.

15   **Table 5**

<u>Plasmid Base</u>

<u>Pair Number:</u>

2 to 881	A transcription termination/polyadenylation signal from the α-subunit of the bovine pituitary glycoprotein hormone (α-FSH) (Goodwin et al., 1983, *Nucleic Acids Res.* <u>11</u>:6873-82; Genbank Accession Number X00004)
882 to 2027	A mouse dihydrofolate reductase (DHFR) minigene containing the endogenous mouse DHFR promoter, the cDNA coding sequences, and the DHFR transcription termination/polyadenylation signals (Gasser et al, 1982, *Proc. Natl. Acad. Sci. U. S. A.* <u>79</u>:6522-6; Nunberg *et al.*, 1980, *Cell* <u>19</u>:355-64; Setzer *et al.*, 1982, *J. Biol. Chem.* <u>257</u>:5143-7; McGrogan *et al.*, 1985, *J. Biol. Chem.* <u>260</u>:2307-14)
2031 to 3947	pBR322 sequences containing the ampicillin resistance marker gene and the origin for replication of the plasmid in *E. coli* (Genbank Accession Number J01749)
3949 to 4292	An SV40 early promoter, enhancer and origin of replication (Takebe *et al.*, 1988, *Mol. Cell Biol.* <u>8</u>:466-72, Genbank Accession Number J02400)
4299 to 4565	A translational enhancer element from the HTLV-1 LTR domain (Seiki *et al.*, 1983, *Proc. Natl. Acad. Sci. U. S. A.* <u>80</u>:3618-22, Genbank Accession Number J02029)

4574 to 4730	An intron from the SV40 16S, 19S splice donor/acceptor signals (Okayama and Berg, 1983, *Mol. Cell Biol.* 3:280-9, Genbank Accession Number J02400)
4755 to 5485	The kappa light chain cDNA between the *Xba*I and *Sal*I sites

Some kappa clones had errors in their constant regions when compared to natural human constant region sequence. To eliminate these discrepancies, the kappa variable region was amplified with a primer that would introduce an *Xba* I site into the 5' end and a *Bsm*B I site into the 3' end. This fragment was then
5   ligated along with a human kappa constant region (Figure 13) with a compatible *Bsm*B I on the 5' end and a 3'*Sal* I ends into pDSRα20 with *Xba* I and *Sal* I ends.

EXAMPLE 5: Transient Expression of Antibodies

This example provides a method of transiently expressing anti-IGF-1R antibodies.
10   The antibodies were expressed transiently in serum-free suspension adapted 293T cells. All transfections were performed as 250 mL cultures. Briefly, 1.25×10^8 cells (5.0×10^5 cells/mL x 250 mL) were centrifuged at 2,500 RPM for 10 minutes at 4° C to remove the conditioned medium. The cells were resuspended in serum-free DMEM and centrifuged again at 2,500 RPM for 10 minutes at 4° C. After aspirating the wash solution, the cells were resuspended in growth medium [DMEM/F12 (3:1) + 1x Insulin-
15   Transferrin-Selenium Supplement + 1X Pen Strep Glut + 2mM L-Glutamine + 20 mM HEPES + 0.01% Pluronic F68] in a 500 mL spinner flask culture. The spinner flask culture was maintained on magnetic stir plate at 125 RPM which was placed in a humidified incubator maintained at 37° C and 5% CO_2. The plasmid DNA was incubated with the transfection reagent in a 50 mL conical tube. The DNA-transfection reagent complex was prepared in 5% of the final culture volume in serum-free DMEM. One microgram of
20   plasmid DNA per milliliter of culture was first added to serum-free DMEM, followed by 1µl X-TremeGene RO-1539/mL culture. The complexes were incubated at room temperature for approximately 30 minutes and then added to the cells in the spinner flask. The transfection/expression was performed for 7 days, after which the conditioned medium was harvested by centrifugation at 4,000 RPM for 60 minutes at 4° C.

If the initial transfection failed to yield the required 100 µg purified antibody, those clones were re-
25   expressed in roller bottles. These transfections used 293T adherent cells grown and maintained in DMEM supplemented with 5% FBS + 1x Non-Essential Amino Acids + 1x Pen Strep Glut + 1x Sodium Pyruvate. Approximately, $4-5 \times 10^7$ 293T cells were seeded in a 850 cm² roller bottles overnight. The previously seeded cells were then transfected the following day using FUGENE™ 6 transfection reagent. The DNA – transfection reagent mixture was prepared in approximately in 6.75 mL serum-free DMEM. 675 µl
30   FUGENE™ 6 transfection reagent was first added, followed by 112.5 µg plasmid DNA. The complex was incubated at room temperature for 30 minutes. The entire mixture was then added to a roller bottle. The roller bottle was infused with a 5% CO_2 gas mixture, capped tightly and placed in a 37° C incubator on a roller rack rotating at 0.35 RPM. The transfection was performed for 24 hours after which the medium was replaced with 100 mL DMEM + 1X Insulin-Transferrin-Selenium Supplement + 1X Pen Strep Glu + 1X
35   Non-Essential Amino Acids + 1X Sodium Pyruvate. Typically, 2-3 harvests (100ml) were obtained from each roller bottle at a 48 hr interval. The harvested serum-free conditioned medium was pooled together and centrifuged at 4,000 RPM for 30 minutes at 4° C.

EXAMPLE 6: Anti-IGF-1R Antibody Small-scale Purification

This example provides a method of purifying anti-IGF-1R antibodies on a small scale.

Conditioned medium was filtered through a 0.45 µm cellulose acetate filter and concentrated approximately 8-fold using a Vivaflow 200 50 K tangential flow membrane (Vivascience, Goettingen,

5   Germany). rProtein A SEPHAROSE™ Fast Flow resin (Amersham Biosciences, Piscataway, NJ) was washed with phosphate buffered saline (2.7 mM potassium chloride, 138 mM sodium chloride, 1.5 mM potassium phosphate, and 8.1 mM sodium phosphate, pH 7.4) (PBS) four times then directly applied to the concentrated media. The amount of resin used was based on antibody concentration determined by ELISA where 1 µl of resin was used per 5 µg antibody. The medium was incubated overnight at 4° C with gentle

10   agitation. The resin was centrifuged at 500 g for 10 min. at 4° C. The supernatant was decanted as the unbound fraction. The resin was washed with PBS four times for one minute at room temperature with gentle agitation, each time collecting the resin by centrifugation at 500 g for 10 min. at 4° C. The antibody was eluted by incubating the resin with 1.5 volumes of 0.1 M glycine pH 3.0 for 10 min. at room temperature. The resin was centrifuged at 500 g for 10 min. at 4° C and the supernatant decanted as eluted

15   antibody. The elution step described above was repeated for a total of three elutions; each time the eluted material was neutralized with 0.04 volumes of 1.0 M tris-HCl, pH 9.2. The sample was filtered through a 0.2 µm cellulose acetate filter. Protein concentration was determined by the Bradford method using the Bio-Rad Protein Assay (Bio-Rad Laboratories, Hercules, CA) as per the supplied instructions using Human IgG (Sigma-Aldrich, St. Louis, MO) as a standard. The sample was compared to a Human IgG1, K

20   standard (Sigma-Aldrich, St. Louis, MO) using a 4-20% tris-glycine SDS polyacrylamide gel (SDS-PAGE) gel stained with Coomassie brilliant blue dye. No contaminating protein was visible in these preparations.

EXAMPLE 7: Isolation of Stable CHO Clones Expressing Antibodies

This example provides a method for isolating stable CHO cell lines expressing anti-IGF-1R

25   antibodies.

Stable expression of TQ11C, TQ25, TQ 58 and TQ59 IgG1 was achieved by co-transfection of AM1-D CHO cells (U.S. Pat. No. 6,210,924, incorporated herein by reference in its entirety) with pDSRα20 heavy and light chian IgG1 expression constructs. The plasmid transfections were performed using LF2000 (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. Briefly, 4 x

30   106AM1-D CHO cells were plated 24 hours prior to transfection, in 100 mm diameter FALCON™ plastic petri dishes (BD Falcon, Franklin Lakes, NJ) in 10 ml of Dulbecco's Modified Eagles Medium (Invitrogen) supplemented with 5% fetal bovine serum, 1x penicillin-streptomycin and glutamine (Invitrogen), non-essential amino acids (Invitrogen), sodium pyruvate, and HT (0.1 mM sodiumhypoxanthine, 16 nM thymidine; Invitrogen). Approximately 15 mg of each pDSRα21 - light chain and heavy chain plasmid

35   DNA were linearized using *Pvu* I (New England Biolabs) and diluted in 2 ml of OPTI-MEM® (Invitrogen). The diluted plasmids were mixed with 75 µl of LIPOFECTAMINE™ 2000 (LF2000; GIBCO/BRL) diluted in 2 ml of OPTI-MEM® and the mixture was incubated for 20 min at room temperature. The following day fresh growth medium was added. The cells were cultured in complete growth medium for 48 hours, then plated in HT- selection medium in 1:20 and 1:50 dilutions. Approximately 2 weeks after transfection, 12-

40   24 visible colonies were picked into 24-well plates, using the sterile cloning discs (RPI). The clones

expressing the highest level of TQ11C, TQ25, TQ58 and TQ59 IgG1 were identified by western immunoblot analysis. To perform this assay, 0.5 ml of serum free medium was added to a single-well confluent cells cultured in a 24 well plate (BD Falcon). The conditioned medium was recovered after 24 hr, and 10 μl of CM was mixed with an equal volume of loading buffer to run a 10% Tris-Glycine

5　polyacrylamide protein gel (Invitrogen). The gel was transferred to a 0.45 μm pore size nitrocellulose membrane (Invitrogen), and western blot analysis was done using 1:1000 dilution of goat anti-human IgG Fc ImmunoPure antibody (Pierce Biotechnology, Inc., Rockford, IL) and ECL as detection agent.

EXAMPLE 8: Mid-scale Expression of Antibodies

10　　　　This example provides a method of expressing anti IGF-1R antibodies expressed by stable CHO cell lines.

　　　　The CHO cell lines made according to Example 7 were expanded to T-175 tissue culture flasks (Falcon) for scale-up expression. A confluent T175 flask (approximately 2 –3 x 107 cells) was used to seed 3 - 850 cm2 roller bottles (Corning Life Sciences, Acton, MA), and three confluent roller bottles

15　(approximately 1-2 x 108 cells per roller bottle) were used to seed 30 rollers in 250 ml of high-glucose DMEM (Invitrogen), 10% dialyzed FBS (Invitrogen), 1x glutamine (Invitrogen), 1x non-essential amino acids (Invitrogen), 1x sodium pyruvate (Invitrogen). Medium was infused with 10% CO_2/balance air for 5 seconds before capping the roller bottle. Roller bottles were incubated at 37° C on roller racks spinning at 0.75 rpm.

20　　　　When cells reached approximately 85-90% confluency (approximately 5-6 days in culture), the growth medium was discarded, the cells were washed with 100 ml PBS, and 200 ml production medium was added (50% DMEM (Invitrogen)/ 50% F12 (Invitrogen), 1x glutamine (Invitrogen), 1x non-essential amino acids (Invitrogen), 1x sodium pyruvate (Invitrogen), 1.5% DMSO (Sigma). Conditioned medium was harvested every seven days for a total of four harvests.

25　　　　Conditioned medium was filtered through a 0.45 μm cellulose acetate filter and concentrated approximately 10-fold using a Sartorius Sartocon Slice Disposable 30 K tangential flow membrane (Sartorius AG, Goettingen, Germany). The concentrated material was applied to a 10 ml rProtein A Sepharose column at 4° C and the flowthrough was collected as the unbound fraction. The column was washed with four column volumes of PBS. The bound sample was eluted with approximately four column

30　volumes of 0.1 M glycine pH 3.0. The eluate peak was collected and neutralized with 0.04 volumes of 1.0 M tris-HCl, pH 9.2. The eluate was dialyzed against 150 volumes of PBS overnight at 4° C. The sample was filtered through a 0.2 μm cellulose acetate filter and protein concentration was measured by determining the absorbance at 280nm using an extinction coefficient of 14,000 M-1. The sample was compared to a Human IgG1, K standard (Sigma-Aldrich, St. Louis, Missouri, USA) using a 4-20% tris-

35　glycine SDS-PAGE gel stained with Coomassie brilliant blue stain. Endotoxin levels in each antibody prepration was determined using the Pyrotell Limulus Amebocyte Lysate Assay (Associates of Cape Cod, Inc., Falmouth, Ma) as per the supplied instructions.

EXAMPLE 9: ORIGEN® Dose Response Competition Assays

This example provides methods for testing the ability of an antibody to block ligand binding to IGF-1R.

An ORIGEN® binding assay was used to determine whether TQ11C, TQ25, TQ 58 and TQ59 IgG1 antibodies could block ligand binding to IGF-1R using procedures provided by the manufacturer

5   (Igen, Inc., Gaithersburg, MD). To label IGF-1 and IGF-2 with ruthenium, lyophilized proteins were dissolved into PBS to give a 1.0 mg/ml solution. Label (ORI-TAG-NHS ester from Igen, Cat # 110034) was added to the protein at a molar ratio of 5:1 (label: protein) from a label stock of 5 mg/ml in DMSO. The mixture was incubated at room temperature (20-22° C) for 1 hr in the dark then treated with 20 µl 2M glycine for 10 min at room temperature. The labeled protein was separated from the free label by

10   application to an Amersham Biosciences NAP-5 column (Amersham Biosciences, Piscataway, NJ) equilibrated in PBS and 0.33 ml fractions collected. The protein concentration of the fractions was determined by Micro BCA Protein Assay (Pierce Biotechnology, Inc., Rockford, IL). Fractions two and three contained significant protein and were combined. The amount of incorporated ruthenium label was assessed using the following formula: ruthenium tris-bipyridyl compound ($Ru(bpy)_3^{2+}$) labeling of IGF-1

15   and IGF-2.

Dynal M450 paramagnetic beads coated with sheep anti-mouse IgG was used as the solid support phase for the IGF-1R(ECD)-C3-muFc. The M450 beads were prepared for receptor loading by washing three times with assay buffer containing 1x PBS, 0.05% TWEEN™ 20 (ICI Americas, Inc., Wilmington DE) 0.1% BSA, 0.01% sodium azide. The IGF-1R(ECD)-C3-muFc was bound for 1 hr at a ratio of 50 ng

20   receptor per 1×10^6 M450 beads in a volume of 25 µl assay buffer. To generate dose response data, the antibodies or unlabeled IGF-1 and IGF-2 factors were added at increasing concentrations (10^{-11}M to 10^{-6}M) simultaneously with 1 nM Ru-IGF-1 or 2 nM Ru-IGF-2. The final reaction volume was 100 µl. After incubation at room temperature in the dark for 2 hr, an M8 Analyzer (Igen) was used to remove free ruthenium labeled ligand and determine the amount of ligand bound to receptor. The data were expressed

25   as the percent of total ligand bound minus background remaining after competition with excess unlabeled growth IGF1 or IGF-2. Competition curves were generated with GraphPad Prism software (GraphPad Software, San Diego, CA) using a single component equilibirium model. Essentially all (> 98%) binding was competed with excess unlabeled growth factors. The positive control antibodies in the binding analysis were the murine anti-IGF-1R antibodies αIR3 (Calbiochem, San Diego, CA) or MAB391 (R&D systems,

30   Minneapolis, MN), 24-57 (Biocarta, San Diego, CA) and 1H7 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA). The negative control antibody was an anti-CD20 antibody. Ligand competition data are shown in Figure 15. The Ki and maximum inhibition values observed for IGF-1 and IGF-2 binding reactions are listed in Table 6.

35   Table 6

Antibody	IGF-1		IGF-2	
	Ki (nM)[1]	Max (%)[2]	Ki (nM)[1]	Max (%)[2]
TQ11C	0.6	84	0.3	91
TQ25	0.8	88	0.8	94

TQ58	0.8	91	0.8	91
TQ59	1.5	79	1.4	91
1H7	16.0	89	13.1	99
αIR3	5.3	91	No Inhibition	

[1] Ki of inhibition.
[2] Maximum level of inhibition at 1 µM antibody concentration.

5   EXAMPLE 10: SPA Dose Response Competition Assay

This example presents a scintillation proximity assay (SPA) for assessing the effect of antibodies on the interaction of insulin (INS) with the insulin receptor (INSR) and of IGF-1 and IGF-2 to IGF-1R.

IGF-1R binding reactions for TQ11C, TQ25, TQ 58 and TQ59 IgG1 antibodies contained 1x PBS, 0,05% TWEEN® 20 (Mallinkrodt), 0.1% BSA (EM Science, Gibbstown, NJ), 50 ng IGF-1R(ECD)-C3-

10   muFc, 500 ug SPA PVT anti-mouse IgG fluoromicrospheres (Amersham) and ^{125}I-labeled IGF-1 or IGF-2 obtained from Amersham at a final concentration of 0.64 nM. The total reaction volume was 100 µl. The INSR binding reactions were identical except they contained 50 ng INSR(ECD)-muFc and 0.64 nM ^{125}I-INS (Amersham). Receptor was loaded onto SPA PVT microspheres for 1h at room temperature prior to assembly of the binding reactions. To generate dose response data, antibodies or unlabeled growth factors

15   were added at increasing concentrations (10^{-11} M to 10^{-6} M) simultaneously with ^{125}I-labeled growth factors. Essentially all binding was competed with excess unlabeled growth factors. The receptor-independent background, caused by random γ stimulation of the SPT PVT microspheres, was less than 0.5% of the input ^{125}I cpm. The data were expressed as the percent of total ligand bound minus background remaining after competition with excess unlabeled growth IGF1 or IGF-2. Competition curves were generated with

20   GraphPad Prism software using a single component equilibrium model.

EXAMPLE 11: Antibody Binding to IGF-1R

This example provides a method of detecting the binding of an anti-IGF-1R antibody to IGF-1R.

BIACORE® 2000, sensor chip CM5, surfactant P20, HBS-EP (10mM HEPES, 0.15M NaCl,

25   3.4mM EDTA, 0.005% P20, pH 7.4), amine coupling kit, 10mM acetate pH 4.5 and 10mM glycine pH 1.5 all were purchased from BIACore, Inc. (Piscataway, NJ). Phosphate-buffered saline (PBS, 1X, no calcium chloride, no magnesium chloride) was from Gibco. Bovine serum albumin (BSA, fraction V, IgG free) was from Sigma. Recombinant Protein G ("rProtein G") was from Pierce Biotechnology.

Immobilization of rProtein G and IGF-1R-C3-muFc to the sensor chip surface was performed

30   according to manufacturer's instructions, using a continuous flow of 10mM HEPES, 0.15M NaCl, 3.4mM EDTA, 0.005% P20, pH 7.4 (HBS-EP buffer). Briefly, carboxyl groups on the sensor chips's surfaces were activated by injecting 60 µl of a mixture containing 0.2 M N-ethyl-N'-(dimethylaminopropyl)carbodiimide (EDC) and 0.05 M N-hydroxysuccinimide (NHS). Specific surfaces were obtained by injecting rProtein A (Pierce) or IGF-1R-C3-mFc diluted in 10mM acetate, pH 4.5 at concentrations between 20 and 50 µg/ml.

35   Excess reactive groups on the surfaces were deactivated by injecting 60 µl of 1 M ethanolamine. Final immobilized levels were 5,000-6,000 resonance units (RU) for the Protein G surfaces, and ~7,800 RU for

the IGF-1R-mFc surfaces. A blank, mock-coupled reference surface was also prepared on the IGF-1R-mFc sensor chip.

The kinetic analysis of the interaction between IGF-1R-mFc and antibodies was performed as follows. Antibodies as well as a positive control antibody (anti-IR3-CDR-human-mouse chimera) were
5   diluted in PBS + 0.005% P20 + 0.1 mg/ml BSA and injected over the Protein G surfaces to capture the antibodies. IGF-1R-mFc was diluted in PBS + 0.005% P20 + 0.1 mg/ml BSA from 500nM to 3.9nM, and each concentration was injected over the captured antibody surfaces, as well as over a blank Protein G surface for background subtraction. After a 10 minute dissociation, each surface was regenerated by injecting 10mM glycine, pH 1.5. Kinetic analysis of the resulting sensorgrams was performed using
10   BIAEvaluation, v. 3.2 (BIACore, Inc.).

A solution affinity analysis was done by incubating two different concentrations (0.2nM and 1nM) of antibody with varying concentrations (0.01nM to 50nM) of IGF-1R-mFc in PBS + 0.005% P-20 + 0.1 mg/ml BSA. Incubations were done at room temperature for at least five hours to allow samples to reach equilibrium. Samples were then injected over the immobilized IGF-1R-mFc surface. After the sample
15   injection, the surfaces were regenerated by injecting 25 μl 8mM glycine, pH 1.5. The binding signal obtained is proportional to the free antibody in solution at equilibrium. The dissociation equilibrium constant (K_D) was obtained from nonlinear regression analysis of the competition curves using a dual-curve one-site homogeneous binding model (KinExA software v. 2.3, Sapidyne Instruments Inc., Boise ID). The data are shown in Table 7
20

Table 7

Antibody	k_{oa} (1/Ms)	K_d (1/s)	Kd (k_a/k_d) Kinetic Method	Kd Equilibrium Method
TQ11C	6.0×10^4	6.7×10^{-5}	1.1 nM	0.3 nM
TQ25	4.4×10^4	$<<5 \times 10^{-5}$		0.10 nM
TQ58	1.1×10^5	2.8×10^{-5}	0.25 nM	0.25 nM
TQ59	6.9×10^4	2.1×10^{-4}	3.0 nM	0.30 nM

EXAMPLE 12: Epitope Mapping Avidin-Fusion proteins

This example provides a method of determining the epitope of IGF-1R bound by an anti-IGF-1R
25   antibody.

The subdomains of IGF-1R bound by antibodies TQ11C, TQ25, TQ58, and TQ59 were determined using avidin-IGF-1R fusion proteins. To express each protein the coding DNA sequences of the complete IGF-1R(ECD) was cloned into the expression vector pCep4-avidin-C such that chicken avidin sequence is joined to the C-terminus of the expressed IGF-1R protein. The ECD coding sequence (1-932)
30   was PCR amplified from a parental IGF-1R plasmid using PCR primers 2804-25:
    5' GCAAGCTTGGGAGAAATCTGCGGGCCAG 3' SEQ ID NO:265
        and 2826-68:
    5' ATTGCGGCCGCTTCATATCCTGTTTTGGCCTG 3' SEQ ID NO:266

72

The primers include a 5' *Hin*d III site and a 3' *Not* I site for cloning into pCep4avidin-C. The amino acid sequence of the avidin-human IGF-1R(ECD) fusion protein is shown in Figure 12. The IGF-1R subdomains constructs used for epitope mapping included: L1 (1-151), CR (152-298), L2 (299-461), FnIII-1 (461-579), FnIII-2/ID (580-798), FnIII-3 (799-901), L1+CR+L2 (1-461), and L1+CR (1-298). The amino acid coordinates of the IGF-1R subdomain represented in each expression plasmid are given in parenthesis. The coding sequence of each domain was PCR amplified from a parental IGF1R cDNA clone using the following primer pairs:

L1:

2804-25: (SEQ ID NO:265)

2804-19:

5' ATTGCGGCCGCCCCACATTCCTTTGGGGGC 3' SEQ ID NO:267

CR:

2804-38:

5' AGCAAGCTTGGACCTGTGTCCAGGGACC 3' SEQ ID NO:268

2804-20:

5' ATTGCGGCCGCGCAAGGACCTTCACAAGGG 3' SEQ ID NO:269

L2:

2804-39:

5' AGCAAGCTTGCCGAAGGTCTGTGAGGAAG 3' SEQ ID NO:270

2804-23:

5' ATTGCGGCCGCACTTTCACAGGAGGCTCTC 3' SEQ ID NO:271

FnIII-1:

2808-08:

5' AGCAAGCTTGGACGTCCTGCATTTCACCTC 3' SEQ ID NO:272

2804-52:

5' ATTGCGGCCGCGGTGCGAATGTACAAGATCTC 3' SEQ ID NO:273

FnIII-2+ID:

2804-41:

5' AGCAAGCTTGAATGCTTCAGTTCCTTCCATTC 3' SEQ ID NO:274

2804-51:

5' ATTGCGGCCGCAGTCCTTGCAAAGACGAAGTTG 3' SEQ ID NO:275

FnIII-3:

2804-42:

5' AGCAAGCTTGATGCCCGCAGAAGGAGCAG 3' SEQ ID NO:276

2804-50:

5' ATTGCGGCCGCTTTAATGGCCACTCTGGTTTC 3' SEQ ID NO:277

L1+CR+L2:

2804-25:

5' AGCAAGCTTGGGAGAAATCTGCGGGCCAG 3' SEQ ID NO:278

2804-23 (SEQ ID NO:272)

L1+CR:

2804-25: AGC AAG CTT GGG AGA AAT CTG CGG GCC AG (SEQ ID NO:279)

2804-20 (SEQ ID NO:270)

     The primers included *Hind* III and *Not* I site for cloning as described for the IGF-1R (ECD). The IGF-1R subdomains were cloned into the expression vector pCep4avidin-N such that chicken avidin sequence (with endogenous signal sequence) is joined to the N-terminus of the expressed IGF-1R proteins.

5   Expression of each avidin-fusion protein was achieved by transient transfection of human 293-EBNA cells (Invitrogen) in roller bottles cultures. The cells were grown and maintained in DMEM supplemented with 5% FBS + 1x Non-Essential Amino Acids + 1x Pen Strep Glut + 1x Sodium Pyruvate. Approximately 4-5 x 10^7 293-EBNA cells were seeded in 850 cm^2 roller bottles overnight. The previously seeded cells were then transfected with pCep4-avidin plasmid DNA the following day using FUGENE™ 6 transfection

10   reagent. The DNA –transfection reagent mixture was prepared in approximately in 6.75 mL serum-free DMEM. 675 µl FUGENE™ 6 transfection reagent was first added, followed by 112.5 µg plasmid DNA. The complex was incubated at room temperature for 30 minutes. The entire mixture was then added to a roller bottle. The roller bottle was gassed with a 5% CO_2 gas mixture, capped tightly and placed in a 37° C incubator on a roller rack rotating at 0.35 RPM. The transfection was performed for 24 hours after which

15   the medium was replaced with 100 mL DMEM + 1X Insulin-Transferrin-Selenium Supplement + 1X Pen Strep Glu + 1X Non-Essential Amino Acids + 1X Sodium Pyruvate. Harvest of the condition medium and replacement with fresh medium occurred 48 hr intervals (2-3 cycles). The harvested serum-free conditioned medium was pooled together and clarified by centrifugation at 10,000 x g for 30 minutes at 4° C.

20   The concentration of avidin-fusion in each conditioned medium was determined using a quantitative FACS based method. The avidin fusion protein in 200 µl of conditioned medium was captured by incubation for 2 hr at room temperature with 5 µl (~ 3.5 x 10^5) of biotin coated polystyrene beads (Spherotech, Inc., Libertyville, IL). The conditioned medium was removed by three cycles of centrifugation and resuspension of the avidin-coated beads in PBS containing 0.5% BSA (BPBS). The

25   avidin-beads were stained with 1 µg/ml of goat FITC-labeled anti-avidin antibody (Vector Lab Burlingame, CA) in 1ml BPBS. After 0.5 hr incubation antibody-beads complexes were collected by centrifugation at 1800 rpm for 5 min and the pellet was washed three times. The FITC fluorescence was detected with a FACSCAN (Beckton Dickson Bioscience, Franklin Lakes, NJ). The signal was converted to protein mass using a standard curve derived with recombinant avidin. For epitope mapping the biotin-beads were loaded

30   with 50-100 ng avidin-fusion protein per ~3.5 x 10^5 beads of beads by incubation with the appropriate amount (1-20 ml) of conditioned medium. The loaded beads were washed extensively and resuspended in 1ml BPBS. For all experiment the biotin-beads were blocked with 10% BSA in PBS prior to loading fusion protein.

     Method 1, One Color Assay: Biotin-coated polystyrene beads loaded with IGF-1R (ECD) and

35   IGF-1R subdomain fusion proteins were mixed with 1 µg of anti-IGF-1R antibody in 1 ml of BPBS. After incubation for 1 hr at room temperature, 4 ml washing buffer was added and the antibody-beads complexes were collected by centrifugation for 5 min at 750g. The pellet was washed 3 times by resuspension in 4 ml of BPBS. The antibody bound to avidin-bead complexes was detected by treatment with 0.5 µg/ml Phycoerythrin-(PE) labeled goat anti-human F(ab')2 (Southern Biotech Associates, Inc., Birmingham, AL)

40   in 1 ml BPBS. Tested antibodies were found to bind to the avidin-fusion protein containing the complete

IGF-1R ECD and the L2 domain. Binding to L1, CR or FnIII-1 was not detected in this experiment. A relatively weak reaction was also observed with the L1 domain.

Method 2, Two color assay: To simultaneously monitor the amounts of anti-IGF-1R monoclonal antibody and avidin-fusion bound to biotin-beads, FITC-labeled anti-avidin antibody was included (1
5 μg/ml) was included in the binding reaction in combination with 0.5 μg/ml PE-labeled goat anti-human IgG1. The beads were prepared for FACSCAN analysis as described for the one color assay.

Method 3, Antibody Competition: To prepare for labeling with fluorescein the antibodies were dialyzed or resuspended at a concentration of 1 mg/ml in PBS (pH 8.5). Label ([6-fluorescein-5-(and-6)-carboxamido] hexanoic acid, succinimidyl ester 5(6)-SFX] mixed isomers from Molecular Probes (Eugene,
10 OR, Cat. No. F2181) was added to the protein at a molar ratio 9.5:1 (label: protein) from a label stock of 5mg/ml in DMSO. The mixture was incubated at 4° C overnight in the dark. The labeled antibody was separated from the free label by dialysis in PBS. The FITC/ antibody ratios obtained ranged from 3 to 8. For each competition experiment, a binding reaction was assembled that contained a 50 fold excess (10-50 μg/ml) of unlabeled competitor antibody, 3.5×10^5 biotin beads coated with avidin fusion protein in BPBS.
15 The FITC-labeled antibody (1 μg/ml) was added after a 30 min preincubation. The process followed the one color method from this point forward.

Each of the four tested antibodies binds to the IGF-1R L2 domain, as shown in Table 8. However, the precise amino acid contacts of each antibody in the IGF-1R L2 domain may differ.

20   Table 8

Antibody	L1[1]	CR[1]	L2[1]	FnIII-1[1]	ECD[1,2]
TQ11C	No	No	Yes	No	Yes
TQ25	No	No	Yes	No	Yes
TQ58	Yes	No	Yes	No	Yes
TQ59	No	No	Yes	No	Yes

[1] Epitope mapping was performed with avidin-IGF-1R fusion proteins containing the indicated human IGF-1R regions.

[2] The ECD fusion contains L1+CR+L2+FnIII-1+FnIII-2+ID+FnIII-3.

25   **EXAMPLE 13: Antibody Binding to Cell-Surface IGF-1R**

This example provides a method for detecting the binding of an anti-IGF-1R antibody to cell-surface expressed IGF-1R.

The ability of antibodies TQ11C, TQ25, TQ58, and TQ59 to bind to human IGF-1R displayed on the cell surface was evaluated using Balb/C 3T3 fibroblasts and MCF-7 human breast cancer cells
30 engineered to overexpress the human IGF-1R receptor at a level of ~3-4 x 10^5 molecules per cell. A Balb/C 3T3 cell line that stably overexpresses the human IGF-1R (~ 3 x10^5 receptors per cell) was derived using with a retroviral vector essentially as described by Pietrzkowski *et al.*, 1992, Cell Growth Differentiation 3:199-205. MCF-7 breast cancer cells that overproduce huIGF-1R were transfected with a pcDNA3.1 expression vector (Invitrogen Corp.). Zeocin resistant cells that express a high level of hu IGF-1R (~4 x

10^5 receptors per cell) were expanded after selection by FACS using anti-IGF-1R monoclonal antibody αIR3 and an PE-labeled goat anti murine IgG antibody (Caltag Laboratories, Burlingame, CA). The process of selection and expansion was repeated four times.

IGF-1R Receptor antibody staining and receptor expression was monitored by FACS as follows: the cells were released from T175 flasks (Corning) by washing 2 times with excess PBS (Ca/Mg free) followed by treatment with 5 ml of Cell Dissociation Buffer (Sigma) for 10 min at room temperature. The cells were collected by centrifugation and washed two times by resuspending them in PBS and centrifugation. For primary antibody staining, 1 μg of antibody was added to 10^6 cells resuspended in 100 μl PBS plus 0.5% BSA (BPBS) and the cells were incubated at 4° C for 1.5 hr. The cells were collected by centrifugation and washed twice with BPBS to remove unbound primary antibody. The cells were resuspended in 100 μl of BPBS and incubated with 1 μg of FITC-labeled goat anti-human F(ab')2 (Southern Biotechnology Associates, Inc., Birmingham, AL) at 4°C for 30 minutes. After washing to remove unbound FITC secondary antibody, the cells were resuspended in 1 ml of PBS+ 0.5% BSA and FITC cell fluorescence was detected with a FACSCAN (Beckton Dickson Bioscience, Franklin Lakes, NJ). The fluorescence levels were converted to absolute receptor levels using Quantum microbead (Bangs Laboratories, Inc., Fishers, IN) with predetermined IgG1 binding capacity to generate a standard curve. Data reduction was performed with QuickCal v2.1 software (Verity Software House, Topsham, ME) provided by the manufacturer.

The peak fluorescent intensity of anti-IGF-1R antibody labeling of the IGF-1R overexpressors was increased 10-20 fold relative to parental Balb/C 3T3 and MCF-7 cells for each of the tested antibodies. This is the result predicted for an antibody that specifically binds IGF-1R. Background fluorescence of cells treated with no antibodies or FITC-labeled secondary alone were insignificant.

EXAMPLE 14: Inhibition of IGF-1R

This example presents methods of detecting inhibition of IGF-1R by anti-IGF-1R antibodies.

32D hu IGF-1R+IRS-1 Cell Inhibition

Murine 32D cells that coexpress the human IGF-1R receptor (20K per cell) and human IRS-1 have proven to be a effective system to examine the molecular components IGF-1R signaling Valentinis *et al.*, 1999, J Biol Chem 274:12423-30. Normal 32D cells express relatively low levels of the murine orthologs of these two gene products. 32D cell normally required IL3 for growth and survival. IGF-1 or IGF-2 can replace IL3 in 32D huIGF-1R+IRS-1 cells as shown in Figure 16, panel A. The EC_{50} to the IGF-1 dose response curve was about 0.5 nM, whereas the IGF-2 EC_{50} (2.8 nM) is about six fold higher reflecting weaker affinity of IGF-2 for IGF-1R. To assess the ability of the antibodies TQ11C, TQ25, TQ58, and TQ59 to block IGF-1 or IGF-2 stimulation, 96-well microtitre plates were seeded with 30,000 32D hu IGF-1R+IRS-1 cells per well in a volume of 200 μl of RPMI (Gibco/BRL) containing 5% fetal bovine serum (Gibco/BRL) and 1x penicillin, streptomycin, glutamine (Giboco/BRL) and increasing concentrations of antibody (10^{-12}M to 10^{-6}M) or no antibody. IGF-1 (2 nM), IGF-2 (8 nM) or nothing was added after 1 hr preincubation with antibody. ^{3}H-thymidine (1 μCi per well) was added at 27 hr post-antibody addition. The cells were harvested 21 hr later, and incorporation of ^{3}H- thymidine into DNA was determined for each

sample. The assays were performed in triplicate. An anti-CD20 antibody was used as a negative control. Each of antibodies TQ11C, TQ25, TQ58, and TQ59 was able to completely block the IGF-1 and IGF-2 mediated stimulation of the 32D cells. The reduction of background proliferation in the absence of added IGF-1 and IGF-2 is due to the inhibition of serum IGF-1 and IGF-2. The binding data were analyzed using

5   GraphPad PRIZM™ software. The data are shown in Figure 16.

Balb/C 3T3 hu IGF-1R Cell Inhibition

        IGF-1 greatly stimulates the incorporation of ^{3}H-thymidine by serum-starved cultures of mouse embryonic fibroblasts (Balb/C 3T3 or NIH 3T3) that overexpress IGF-1R (~1 x 10^6 IGF1R per cell). Kato

10   *et al.*, 1993, J Biol Chem 268:2655-61; Pietrzkowski *et al.*, 1992, Cell Growth Differentiation 3:199-205. This phenomenon is recapitulated with both IGF-1 and IGF-2 in a Balb/C 3T3 cell line hu IGF-1R overexpressor. Both growth factors stimulated ^{3}H-thymidine incorporation by about 20-fold. The EC_{50} of the IGF-1 dose response curve was about 0.7 nM, whereas the IGF-2 EC_{50} (4.4 nM) is sevenfold higher, indicating a weaker affinity of IGF-2 for IGF-1R. To assess the ability of a given antibody to block IGF-1

15   or IGF-2 stimulation, 96-well microtitre plates were seeded with 10,000 cells per well in a volume of 200 μl of DMEM (Gibco/BRL) containing 10% calf serum (Gibco/BRL) and 1x penicillin, streptomycin, glutamine (Giboco/BRL). After overnight incubation when the cells were about 80% confluent the growth medium was replaced with 100 μl DMEM containing 0.1% BSA after washing once with 200 μl PBS. Antibodies at increasing concentrations (10^{-12} M to 10^{-6} M), or no antibody, were added at 24 hr post-serum

20   starvation. IGF-1 (2 nM), IGF-2 (8 nM) and ^{3}H-thymindine (1 μCi per well) were added after a 1 hr preincubation with antibody. The cells were harvested 24 hr later, and incorporation of ^{3}H- thymidine into DNA was determined for each sample. The assays were performed in triplicate. Each tested antibody was able to completely block the IGF-1 and IGF-2 mediated stimulation of Balb/C 3T3 cells, as shown in Figure 17. An anti-CD20 antibody was used as a negative control ("CD20" in Figure 17).

25

        Each reference cited herein is incorporated by reference in its entirety for all that it teaches and for all purposes.

What is claimed is:

1. An isolated antigen binding protein comprising either:

        a. a light chain CDR3 comprising a sequence selected from the group consisting of:

        i. a light chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence selected from the group consisting of the light chain CDR3 sequences of L1-L52 as shown in Figure 6;

            ii. $M\ X_1\ X_2\ X_3\ X_4\ X_5\ P\ X_6\ X_7$;

            iii. $Q\ Q\ X_8\ X_9\ X_{10}\ X_{11}\ P\ X_{12}\ T$; and

            iv. $Q\ S\ Y\ X_{13}\ X_{14}\ X_{15}\ N\ X_{16}\ X_{17}\ X_{18}$;

        b. a heavy chain CDR3 comprising a sequence selected from the group consisting of:

        i. a heavy chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence selected from the group consisting of the heavy chain CDR3 sequences of H1-H52 as shown in Figure 9;

            ii. $X_{19}\ X_{20}\ X_{21}\ X_{22}\ X_{23}\ X_{24}\ X_{25}\ X_{26}\ X_{27}\ F\ D\ I$;

            iii. $X_{28}\ X_{29}\ X_{30}\ X_{31}\ X_{32}\ X_{33}\ X_{34}\ X_{35}\ X_{36}\ X_{37}\ X_{38}\ M\ D\ V$;

            iv. $D\ S\ S\ X_{39}$; or

        c. the light chain CDR3 sequence of (a) and the heavy chain CDR3 sequence of (b);

wherein

        X_1 is a glutamine residue or a glutamate residue,

        X_2 is an alanine residue, a glycine residue, a threonine residue, or a serine residue,

        X_3 is a leucine residue, a phenylalanine residue, or a threonine residue,

        X_4 is glutamine residue, a glutamate residue, or a histidine residue,

        X_5 is a threonine residue, a methionine residue, a tryptophan residue, or a valine residue,

        X_6 is a glycine residue, an alanine residue, a valine residue, a leucine residue, an isoleucine residue, a proline residue, a phenylalanine residue, a methionine residue, a tryptophan residue, or a cysteine residue,

        X_7 is threonine residue, an alanine residue, or a serine residue,

        X_8 is an arginine residue, a serine residue, a leucine residue, or an alanine residue,

        X_9 is an asparagine residue, a serine residue, or a histidine residue,

        X_{10} is an asparagine residue or a serine residue,

        X_{11} is a tryptophan residue, a valine residue, a tyrosine residue, a proline residue, or a phenylalanine residue,

        X_{12} is a leucine residue, a tyrosine residue, or an isoleucine residue,

        X_{13} is an aspartate residue or a glutamine residue,

        X_{14} is a serine residue or a proline residue,

        X_{15} is a serine residue, a tyrosine residue, an aspartate residue, or an alanine residue,

        X_{16} is a glutamine residue, an arginine residue, a valine residue, or a tryptophan residue,

        X_{17} is an arginine residue, a valine residue, an isoleucine residue, or no residue,

        X_{18} is a valine residue or no residue,

X_{19} is a glutamate residue or no residue,

X_{20} is a tyrosine residue, a glycine residue, a serine residue, or no residue,

X_{21} is a serine residue, an asparagine residue, a tryptophan residue, a glutamate residue, as aspartate residue, or no residue,

X_{22} is a serine residue, an aspartate residue, a tryptophan residue, an alanine residue, an arginine residue, a threonine residue, a glutamine residue, a leucine residue, a glutamate residue, or no residue,

X_{23} is a serine residue, a glycine residue, an asparagine residue, a threonine residue, a tryptophan residue, a valine residue, an alanine residue, or an isoleucine residue,

X_{24} is an arginine residue, a glutamine residue, a tyrosine residue, a valine residue, an alanine residue, a glycine residue, a serine residue, a phenylalanine residue, or a tryptophan residue,

X_{25} is an asparagine residue, a leucine residue, an aspartate residue, a threonine residue, a tryptophan residue, a tyrosine residue, a valine residue, an alanine residue, or a histidine residue,

X_{26} is an aspartate residue, a serine residue, an asparagine residue, or a glutamine residue,

X_{27} is an alanine residue or a proline residue,

X_{28} is an alanine residue or no residue,

X_{29} is a glutamate residue, a tyrosine residue, a glycine residue, or no residue,

X_{30} is an arginine residue, a serine residue, or no residue,

X_{31} is a glycine residue, an aspartate residue, a valine residue, a serine residue, or no residue,

X_{32} is a serine residue, an aspartate residue, a glycine residue, or no residue,

X_{33} is a phenylalanine residue, an aspartate residue, a tyrosine residue, a glycine residue, a serine residue, a histidine residue, a tryptophan residue, or no residue,

X_{34} is a tryptophan residue, an aspartate residue, a tyrosine residue, a serine residue, or no residue,

X_{35} is an aspartate residue, a glutamate residue, an arginine residue, a serine residue, a glycine residue, a tyrosine residue, or a tryptophan residue,

X_{36} is a tyrosine residue, a lysine residue, an isoleucine residue, a leucine residue or a phenylalanine residue,

X_{37} is a tyrosine residue, a serine residue, a phenylalanine residue, an aspartate residue, or a glycine residue,

X_{38} is a glycine residue, an asparagine residue, or a tyrosine residue,

X_{39} is a valine residue, a glycine residue, or a serine residue,

and said antigen binding protein binds specifically to human IGF-1R.

2. The isolated antigen binding protein of Claim 1, comprising an amino acid sequence selected from the group consisting of:

     a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;

     b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;

c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;

d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;

e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and

f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

3. The isolated antigen binding protein of Claim 2, comprising an amino acid sequence selected from the group consisting of:

a. a light chain CDR1 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;

b. a light chain CDR2 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR2 sequence of L1-L52 as shown in Figure 5;

c. a light chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;

d. a heavy chain CDR1 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR1 sequence of H1-H52 as shown in Figure 7;

e. a heavy chain CDR2 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and

f. a heavy chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

4. The isolated antigen binding protein of Claim 3, comprising an amino acid sequence selected from the group consisting of:

a. a light chain CDR1 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;

b. a light chain CDR2 sequence of L1-L52 as shown in Figure 5;

c. a light chain CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of L1-L52 as shown in Figure 6;

d. a heavy chain CDR1 sequence of H1-H52 as shown in Figure 7;

e. a heavy chain CDR2 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and

f. a heavy chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

5. The isolated antigen binding protein of Claim 4, comprising an amino acid sequence selected from the group consisting of:

a. a light chain CDR1 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;

b. a light chain CDR3 sequence of L1-L52 as shown in Figure 6;

c. a heavy chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and

d. a heavy chain CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of H1-H52 as shown in Figure 9.

6. The isolated antigen binding protein of Claim 5, comprising an amino acid sequence selected from the group consisting of:

a. a light chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;

b. a heavy chain CDR2 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR2 sequence of H1-H52 as shown in Figure 8; and

c. a heavy chain CDR3 sequence of H1-H52 as shown in Figure 9.

7. The isolated antigen binding protein of Claim 6, comprising an amino acid sequence selected from the group consisting of:

a. a light chain CDR1 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR1 sequence of L1-L52 as shown in Figure 4; and

b. a heavy chain CDR2 sequence of H1-H52 as shown in Figure 8.

8. The isolated antigen binding protein of Claim 7, comprising a CDR1 sequence of L1-L52 as shown in Figure 4.

9. The isolated antigen binding protein of Claim 1, comprising a sequence selected from the group consisting of:

a. a light chain CDR1 sequence selected from the group consisting of:

    i. RSSQSLLHSNGYNYLD;

    ii. RASQ(G/S)(I/V)(G/S)X(Y/F)L(A/N); and

    iii. RSSQS(L/I)XXXXX;

b. a light chain CDR2 sequence selected from the group consisting of:

    i. LGSNRAS;

    ii. AASTLQS; and

    iii. EDNXRPS;

c. a heavy chain CDR1 sequence selected from the group consisting of:

    i. SSNWWS;

    ii. XYYWS; and

    iii. SYAM(S/H); and

d. a heavy chain CDR2 sequence selected from the group consisting of:

      i.   (E/I)(I/V)(Y/N)(H/Y)SGST(N/Y)YNPSLKS; and

      ii. XIS(G/S)SG(G/S)STYYADSVKG;

wherein amino acid residue symbols enclosed in parentheses identify alternative residues for the same position in a sequence, each X is independently any amino acid residue, and each Z is independently a glycine residue, an alanine residue, a valine residue, a leucine residue, an isoleucine residue, a proline residue, a phenylalanine residue, a methionine residue, a tryptophan residue, or a cysteine residue.

10. The isolated antigen binding protein of Claim 1, comprising a heavy chain CDR3 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

11. The isolated antigen binding protein of Claim 10, comprising a heavy chain CDR3 sequence that differs by no more than a total of one amino acid addition, substitution, or deletion from a CDR3 sequence of H1-H52 as shown in Figure 9.

12. The isolated antigen binding protein of Claim 11, comprising a heavy chain CDR3 sequence of H1-H52 as shown in Figure 9.

13. The isolated antigen binding protein of Claim 1, comprising two amino acid sequences selected from the group consisting of:

      a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;

      b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;

      c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;

      d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;

      e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and

      f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

14. The isolated antigen binding protein of Claim 13, comprising three amino acid sequences selected from the group consisting of:

      a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;

      b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;

c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;

d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;

e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and

f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

15. The isolated antigen binding protein of Claim 14, comprising four amino acid sequences selected from the group consisting of:

a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;

b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;

c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;

d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;

e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and

f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

16. The isolated antigen binding protein of Claim 15, comprising five amino acid sequences selected from the group consisting of:

a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;

b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;

c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;

d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;

e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and

f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

17. The isolated antigen binding protein of Claim 16, comprising:

      a. a light chain CDR1 sequence that differs by no more than a total of six amino acid additions, substitutions, and/or deletions from a CDR1 sequence of L1-L52 as shown in Figure 4;

      b. a light chain CDR2 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR2 sequence of L1-L52 as shown in Figure 5;

      c. a light chain CDR3 sequence that differs by no more than a total of three amino acid additions, substitutions, and/or deletions from a CDR3 sequence of L1-L52 as shown in Figure 6;

      d. a heavy chain CDR1 sequence that differs by no more than a total of two amino acid additions, substitutions, and/or deletions from a CDR1 sequence of H1-H52 as shown in Figure 7;

      e. a heavy chain CDR2 sequence that differs by no more than a total of five amino acid additions, substitutions, and/or deletions from a CDR2 sequence of H1-H52 as shown in Figure 8; and

      f. a heavy chain CDR3 sequence that differs by no more than a total of four amino acid additions, substitutions, and/or deletions from a CDR3 sequence of H1-H52 as shown in Figure 9.

18. The isolated antigen binding protein of Claim 1, comprising either:

      a. a light chain variable domain comprising:

          i. a light chain CDR1 sequence shown in Figure 4;

          ii. a light chain CDR2 sequence shown in Figure 5; and

          iii. a light chain CDR3 sequence shown in Figure 6;

      b. a heavy chain variable domain comprising:

          i. a heavy chain CDR1 sequence shown in Figure 7;

          ii. a heavy chain CDR2 sequence shown in Figure 8; and

          iii. a heavy chain CDR3 sequence shown in Figure 9; or

      c. the light chain variable domain of (a) and the heavy chain variable domain of (b).

19. The isolated antigen binding protein of Claim 18, comprising either:

      a. light chain CDR1, CDR2, and CDR3 sequences that each is identical to the CDR1, CDR2, and CDR3 sequences, respectively, of the same light chain variable domain sequence selected from the group consisting of L1-L52;

      b. heavy chain CDR1, CDR2, and CDR3 sequences that each is identical to the CDR1, CDR2, and CDR3 sequences, respectively, of the same heavy chain variable domain sequence selected from the group consisting of H1-H52; or

      c. the light chain CDR1, CDR2, and CDR3 sequences of (a) and the heavy chain CDR1, CDR2, and CDR3 sequences of (b).

20. An isolated antigen binding protein comprising either:

      a. a light chain variable domain sequence selected from the group consisting of:

      i. a sequence of amino acids at least 80% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;

      ii. a sequence of amino acids comprising at least 15 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2;

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and

iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of a light chain variable domain sequence of L1-L52 as shown in Figure 1;

b. a heavy chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 80% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 15 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; and

iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under moderately stringent conditions to the complement of a polynucleotide consisting of a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or

c. the light chain variable domain of (a) and the heavy chain variable domain of (b);

wherein said antigen binding protein binds to human IGF-1R.

21. The isolated antigen binding protein of Claim 20, comprising either:

a. a light chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 85% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 25 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2;

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 85% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and

iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under highly stringent conditions to the complement of a polynucleotide consisting of a light chain variable domain sequence of L1-L52 as shown in Figure 1;

b. a heavy chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 85% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 25 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 85% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; and

iv. a sequence of amino acids encoded by a polynucleotide sequence that hybridizes under highly stringent conditions to the complement of a polynucleotide consisting of a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or

c) the light chain variable domain of (a) and the heavy chain variable domain of (b).

22. The isolated antigen binding protein of Claim 21, comprising either:

a. a light chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 90% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 35 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 90% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and

b. a heavy chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 90% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 35 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 90% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or

c) the light chain variable domain of (a) and the heavy chain variable domain of (b).

23. The isolated antigen binding protein of Claim 22, comprising either:

a. a light chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 95% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 50 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 95% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and

b. a heavy chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 95% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 50 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 95% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or

c) the light chain variable domain of (a) and the heavy chain variable domain of (b).

24. The isolated antigen binding protein of Claim 23, comprising either:

a. a light chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 97% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 75 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 97% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and

b. a heavy chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 97% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 75 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 97% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or

c) the light chain variable domain of (a) and the heavy chain variable domain of (b).

25. The isolated antigen binding protein of Claim 24, comprising either:

a. a light chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 99% identical to a light chain variable domain sequence of L1-L52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 90 contiguous amino acid residues of a light chain variable domain sequence of L1-L52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 99% identical to a polynucleotide sequence encoding a light chain variable domain sequence of L1-L52 as shown in Figure 1; and

b. a heavy chain variable domain sequence selected from the group consisting of:

i. a sequence of amino acids at least 99% identical to a heavy chain variable domain sequence of H1-H52 as shown in Figure 2;

ii. a sequence of amino acids comprising at least 90 contiguous amino acid residues of a heavy chain variable domain sequence of H1-H52 as shown in Figure 2; and

iii. a sequence of amino acids encoded by a polynucleotide sequence that is at least 99% identical to a polynucleotide sequence encoding a heavy chain variable domain sequence of H1-H52 as shown in Figure 1; or

    c. the light chain variable domain of (a) and the heavy chain variable domain of (b).

26. The isolated antigen binding protein of Claim 25 comprising either:

    a. a light chain variable domain sequence selected from the group consisting of L1-L52 as shown in Figure 2;

    b. a heavy chain variable domain sequence selected from the group consisting of H1-H52 as shown in Figure 3; or

    c. the light chain variable domain of (a) and the heavy chain variable domain of (b).

27. The isolated antigen binding protein of Claim 26 comprising a combination of a light chain variable domain and a heavy chain variable domain selected from the group of combinations consisting of: L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20, H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52.

28. The isolated antigen binding protein of Claim 27 further comprising:

    a.   the kappa light chain constant sequence of Figure 13,

    b.   the IgG1 heavy chain constant sequence of Figure 13, or

    c.   the kappa light chain constant sequence of Figure 13 and the IgG1 heavy chain constant sequence of Figure 13.

29. The isolated antigen binding protein of Claim 1 or Claim 20, that, when bound to IGF-1R:

    a. inhibits IGF-1R;

    b. activates IGF-1R;

    c. cross-competes with a reference antibody for binding to IGF-1R;

    d. binds to the same epitope of IGF-1R as said reference antibody;

    e. binds to IGF-1R with substantially the same Kd as said reference antibody; or

    f. binds to IGF-1R with substantially the same off rate as said reference antibody;

wherein said reference antibody comprises a combination of light chain and heavy chain variable domain sequences selected from the group of combinations consisting of L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20, H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46, L47H47, L48H48, L49H49, L50H50, L51H51, and L52H52.

30. The isolated antigen binding protein of Claim 1 or Claim 20, that, when bound to a human IGF-1R, inhibits binding of IGF-1 and/or IGF-2 to said human IGF-1R.

31. The isolated antigen binding protein of Claim 1 or Claim 20, that inhibits the growth of a cancer cell by greater than about 80% in the presence of a growth stimulant selected from the group consisting of serum, IGF-1, and IGF-2.

32. The isolated antigen binding protein of Claim 31, wherein said cancer cell is an MCF-7 human breast cancer cell.

33. The isolated antigen binding protein of Claim 1 or Claim 20, that binds to human IGF-1R with a selectivity that is at least fifty times greater than its selectivity for human insulin receptor.

34. The isolated antigen binding protein of Claim 1 or Claim 20, that inhibits tumor growth *in vivo*.

35. The isolated antigen binding protein of Claim 1 or Claim 20, that inhibits IGF-1R mediated tyrosine phosphorylation.

36. The isolated antigen binding protein of Claim 1 or Claim 20, that specifically binds to the IGF-1R of a non-human primate, a cynomologous monkey, a chimpanzee, a non-primate mammal, a rodent, a mouse, a rat, a hamster, a guinea pig, a cat, or a dog.

37. The isolated antigen binding protein of Claim 1 or Claim 20 wherein said antigen binding protein comprises:

       a. a human antibody;

       b. a humanized antibody;

       c. a chimeric antibody;

       d. a monoclonal antibody;

       e. a polyclonal antibody;

       f. a recombinant antibody;

       g. an antigen-binding antibody fragment;

       h. a single chain antibody;

       i. a diabody;

       j. a triabody;

       k. a tetrabody;

       l. a Fab fragment;

       m. a $F(ab')_2$ fragment;

       n. a domain antibody;

       o. an IgD antibody;

p. an IgE antibody;

q. an IgM antibody;

r. an IgG1 antibody;

s. an IgG2 antibody;

t. an IgG3 antibody;

u. an IgG4 antibody; or

v. an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond.

38. An isolated polynucleotide comprising a sequence that encodes the light chain, the heavy chain, or both of said antigen binding protein of Claim 1 or Claim 20.

39. The isolated polynucleotide of Claim 38, wherein said polynucleotide comprises a light chain variable domain nucleic acid sequence of Figure 1 and/or a heavy chain variable domain nucleic acid sequence of Figure 1.

40. A plasmid comprising said isolated polynucleotide of Claim 38.

41. The plasmid of Claim 40, wherein said plasmid is an expression vector.

42. An isolated cell comprising said polynucleotide of Claim 38.

43. The isolated cell of Claim 42, wherein a chromosome of said cell comprises said polynucleotide.

44. The isolated cell of Claim 42, wherein said cell is a hybridoma.

45. The isolated cell of Claim 42, wherein an expression vector comprises said polynucleotide.

46. The isolated cell of Claim 42, wherein said cell is a CHO cell.

47. A method of making an antigen binding protein that binds human IGF-1R, comprising incubating said isolated cell of Claim 42 under conditions that allow it to express said antigen binding protein.

48. A pharmaceutical composition comprising the antigen binding protein of Claim 1 or Claim 20.

49. A method of treating a condition in a subject comprising administering to said subject said pharmaceutical composition of Claim 48, wherein said condition is treatable by reducing the activity of IGF-1R in said subject.

50. The method of Claim 49 wherein said subject is a human being.

51. The method of Claim 49 wherein said condition is multiple myeloma, a liquid tumor, liver cancer, a thymus disorder, a T-cell mediated autoimmune disease, an endocronological disorder, ischemia, or a neurodegenerative disorder.

52. The method of claim 51 wherein said liquid tumor is selected from the group consisting of acute lymphocytic leukemia (ALL) and chronic myelogenous leukemia (CML); wherein said liver cancer is selected from the group consisting of hepatoma, hepatocellular carcinoma, cholangiocarcinoma, angiosarcomas, hemangiosarcomas, hepatoblastoma; wherein said thymus disorder is selected from the group consisting of thymoma and thyroiditis, wherein said T-cell mediated autoimmune disease is selected from the group consisting of Multiple Sclerosis, Rheumatoid Arthritis, Systemic Lupus Erythematosus (SLE), Grave's Disease, Hashimoto's Thyroiditis, Myasthenia Gravis, Auto-Immune Thyroiditis, Bechet's Disease, wherein said endocrinological disorder is selected from the group consisting of Type II Diabetes, hyperthyroidism, hypothyroidism, thyroiditis, hyperadrenocorticism, and hypoadrenocorticism; wherein said ischemia is post cardiac infarct ischemia, or wherein said neurodegenerative disorder is Alzheimer's Disease.

53. The method of Claim 49 wherein said condition is selected from the group consisting of acromegaly, bladder cancer, Wilm's tumor, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervical cancer, synovial sarcoma, diarrhea associated with metastatic carcinoid, vasoactive intestinal peptide secreting tumors, gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels, inappropriate microvascular proliferation, glioblastoma, medulloblastoma, head and neck squamous cell cancer, oral cancer, oral leukoplakia, prostate intraepithelial neoplasia, anal cancer, esophageal cancer, gastric cancer, bone cancer, metastatic cancer, polycythemia rubra vera, a benign condition related to oxidative stress, retinopathy of prematurity, Acute Respiratory Distress Syndrome, an overdose of acetaminophen, bronchopulmonary dysplasia, cystic fibrosis, lung fibrosis, and diabetic retinopathy.

54. The method of Claim 49 further comprising administering to said subject a second treatment.

55. The method of Claim 54 wherein said second treatment is administered to said subject before and/or simultaneously with and/or after said pharmaceutical composition is administered to said subject.

56. The method of Claim 54 wherein said second treatment comprises radiation treatment, surgery, or a second pharmaceutical composition.

57. The method of Claim 56 wherein said second pharmaceutical composition comprises an agent selected from the group consisting of a corticosteroid, an anti-emetic, ondansetron hydrochloride, granisetron hydrochloride, metroclopramide, domperidone, haloperidol, cyclizine, lorazepam, prochlorperazine, dexamethasone, levomepromazine, tropisetron, a cancer vaccine, a GM-CSF inhibiting agent, a GM-CSF

DNA vaccine, a cell-based vaccine, a dendritic cell vaccine, a recombinant viral vaccine, a heat shock protein (HSP) vaccine, an allogeneic tumor vaccine, an autologous tumor vaccine, an analgesic, ibuprofen, naproxen, choline magnesium trisalicylate, an oxycodone hydrochloride, an anti-angiogenic agent, an anti-vascular agent, bevacizumab, an anti-VEGF antibody, an anti-VEGF receptor antibody, a soluble VEGF receptor fragment, an anti-TWEAK antibody, an anti-TWEAK receptor antibody, a soluble TWEAK receptor fragment, AMG 706, AMG 386, an anti-proliferative agent, a farnesyl protein transferase inhibitor, an αvβ3 inhibitor, an αvβ5 inhibitor, a p53 inhibitor, a Kit receptor inhibitor, a ret receptor inhibitor, a PDGFR inhibitor, a growth hormone secretion inhibitor, an angiopoietin inhibitor, a tumor infiltrating macrophage-inhibiting agent, a c-fms inhibiting agent, an anti-c-fms antibody, an CSF-1 inhibiting agent, an anti-CSF-1 antibody, a soluble c-fms fragment, pegvisomant, gemcitabine, panitumumab, irinothecan, and SN-38.

58. The method of Claim 54 further comprising administering to said subject a third treatment.

59. The method of Claim 58, wherein said condition is a cancer, said second treatment comprises administering panitumumab, and said third treatment comprises administering gemcitabine.

60. The method of Claim 49 wherein said condition is selected from the group consisting of acromegaly, bladder cancer, Wilm's tumor, ovarian cancer, pancreatic cancer, benign prostatic hyperplasia, breast cancer, prostate cancer, bone cancer, lung cancer, colorectal cancer, cervical cancer, synovial sarcoma, diarrhea associated with metastatic carcinoid, vasoactive intestinal peptide secreting tumors, gigantism, psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels, inappropriate microvascular proliferation, glioblastoma, medulloblastoma, head and neck squamous cell cancer, oral cancer, oral leukoplakia, prostate intraepithelial neoplasia, anal cancer, esophageal cancer, gastric cancer, bone cancer, metastatic cancer, polycythemia rubra vera, a benign condition related to oxidative stress, retinopathy of prematurity, Acute Respiratory Distress Syndrome, an overdose of acetaminophen, bronchopulmonary dysplasia, cystic fibrosis, lung fibrosis, and diabetic retinopathy.

61. A method of increasing the longevity of a subject comprising administering to said subject said pharmaceutical composition of Claim 48.

62. A method of decreasing IGF-1R activity in a subject in need thereof comprising administering to said subject said pharmaceutical composition of Claim 48.

63. A method of decreasing IGF-1R signaling in a subject in need thereof comprising administering to said subject said pharmaceutical composition of Claim 48.

64. A method of inhibiting the binding of IGF-1 and/or IGF-2 to IGF-1R in a subject in need thereof comprising administering to said subject said pharmaceutical composition of Claim 48.

Figure 1

L1 (SEQ ID NO:1)
```
    GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC
TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAGTGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC
CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTCAG
TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT
TACTGCATGC AAGCTCTACA AACTCCGATC ACCTTCGGCC AAGGGACACG ACTGGAGATT AAA
```

L2 (SEQ ID NO:3)
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    GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC
TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC
CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTCAG
TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT
TACTGCATGC AAGCTCTACA AACTCCGATC ACCTTCGGCC AAGGGACACG ACTGGAGATT AAA
```

L3 (SEQ ID NO:5)
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    GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC
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CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTCAG
TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT
TACTGCATGC AAGCTCTACA AACTCCACTC ACTTTCGGCG GCGGGACCAA GGTGGAGATC AAA
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L4 (SEQ ID NO:7)
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    GA AATTGTGATG ACGCAGTCTC CACTCTCCCT GCCCGTCACC CCTGGAGAGC CGGCCTCCAT
CTCCTGCAGG TCTAGTCAGA GCCTCCTGCA TAGTAATGGA TACAACTATT TGGATTGGTA CCTGCAGAAG
CCAGGGCAGT CTCCACAGCT CCTGATCTAT TTGGGTTCTA ATCGGGCCTC CGGGGTCCCT GACAGGTTCA
GTGGCAGTGG ATCAGGCACA GATTTTACAC TGAAAATCAG CAGAGTGGAG GCTGAGGATG TTGGGGTTTA
TTACTGCATG CAAGCTCTAC AAACTCCTCA CACTTTCGGC GGAGGGACCA AGGTGGAGAT CAAA
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L5 (SEQ ID NO:9)
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    GAAA TTGTGCTGAC TCAGTCTCCA CTCTCCCTGC CCGTCACCCC TGGAGAGCCG GCCTCCATCT
CCTGCAGGTC TAGTCAGAGC CTCCTGCATA GTAATGGATA CAACTATTTG GATTGGTACC TGCAGAAGCC
AGGGCAGTCT CCACAGCTCC TGATCTATTT GGGTTCTAAT CGGGCCTCCG GGGTCCCTGA CAGGTTCAGT
GGCAGTGGAT CAGGCACAGA TTTTACACTG AAAATCAGCA GAGTGGAGGC TGAGGATGTT GGGGTTTATT
ACTGCATGCA AGCTCTACAA ACCCCTCTCA CTTTCGGCCC TGGGACCAAA GTGGATATCA AA
```

L6 (SEQ ID NO:11)
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    GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG GCCGTCACCC CTGGAGAGCC GGCCTCCATC
TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC
CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTCAG
TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT
TACTGCATGC AAGCTCTACA AACTCCGCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA
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L7 (SEQ ID NO:13)
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    GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC
TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC
CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTCAG
TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT
TACTGCATGC AAGCTCTACA AACTCCTCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA
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L8 (SEQ ID NO:15)
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 GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC
AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC
AGTCTCCACA GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGGCAG
TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAAG ATGTTGGGGT TTATTACTGT
ATGCAAGCTC TACAAACCCC CCTCACTTTC GGCGGAGGGA CCAAGGTGGA GATCAAA
```

L9 (SEQ ID NO:17)
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    GATG TTGTGATGAC TCAGTCTCCA CTCTCCCTGC CCGTCACCCC TGGAGAGCCG GCCTCCATCT
CCTGCAGGTC TAGTCAGAGC CTCCTGCATA GTAATGGATA CAACTATTTG GATTGGTACC TGCAGAAGCC
AGGGCAGTCT CCACAGCTCC TGATCTATTT GGGTTCTAAT CGGGCCTCCG GGGTCCCTGA CAGGTTCAGT
GGCAGTGGAT CAGGCACAGA TTTTACACTG AAAATCAGCA GAGTGGAGGC TGAGGATGTT GGGGTTTATT
ACTGCATGCA AGCTCTACAA ACTCCGTTCA CCTTCGGCCA AGGGACACGA CTGGAGATTA AA
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L10 (SEQ ID NO:19)
GATGTTGTGA TGACTCAGTC TCCACTCTCC CTGCCCGTCA CCCCTGGAGA GCCGGCCTCC ATCTCCTGCA
GGTCTAGTCA GAGCCTCCTG CATAGTAATG GATACAACTA TTTGGATTGG TACCTGCAGA AGCCAGGGCA
GTCTCCACAG CTCCTGATCT ATTTGGGTTC TAATCGGGCC TCCGGGGTCC CTGACAGGTT CAGTGGCAGT
GGATCAGGCA CAGATTTTAC ACTGAAAATC AGCAGAGTGG AGGCTGAGGA TGTTGGGGTT TATTACTGCA
TGCAAGCTCT ACAAACTCCT CTGGCGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAA

L11 (SEQ ID NO:21)
 GAAATTGT GCTGACTCAG TCTCCACTCT CCCTGCCCGT CACCCCTGGA GAGCCGGCCT CCATCTCCTG
CAGGTCTAGT CAGAGCCTCC TGCATAGTAA TGGATACAAC TATTTGAATT GGTACCTGCA GAAGCCAGGG
CAGTCTCCAC AGCTCCTGAT CTATTTGGGT TCTAATCGGG CCTCCGGGGT CCCTGACAGG TTCAGTGCCA
GTGGATCAGG CACAGATTTT ACACTGAAAA TCAGCAGAGT GGAGGCTGAG GATGTTGGGG TTTATTACTG
CATGCAAGCT CTACAAACTC CTATCACCTT CGGCCAAGGG ACACGACTGG AGATTAAA

L12 (SEQ ID NO:23)
     AATT TTATGCTGAC TCAGCCCCAC TCTGTGTCGG AGTCTCCGGG GAAGACGGTA ACCATCTCCT
GCACCCGCAG CAGTGGCAGC ATTGCCAGCA ACTATGTGCA GTGGTACCAG CAGCGCCCGG GCAGTTCCCC
CACCACTGTG ATCTATGAGG ATAACCAAAG ACCCTCTGGG GTCCCTGATC GGTTCTCTGG CTCCATCGAC
AGCTCCTCCA ACTCTGCCTC CCTCACCATC TCTGGACTGA AGACTGAGGA CGAGGCTGAC TACTACTGTC
AGTCTTATGA TAGCAGCAAT CAGAGAGTGT TCGGCGGAGG GACCAAGCTG ACCGTCCTA

L13 (SEQ ID NO:25)
      GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC
TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC
CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTCAG
TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT
TACTGCATGC AAGCTCTACA AACCCCGCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

L14 (SEQ ID NO:27)
        G ATGTTGTGAT GACTCAGTCT CCACTCTCCC TGCCCGTCAC CCCTGGAGAG CCGGCCTCCA
TCTCCTGCAG GTCTAGTCAG AGCCTCCTGC ATAGTAATGG ATACAACTAT TTGGATTGGT ACCTGCAGAA
GCCAGGGCAG TCTCCACAGC TCCTGATCTA TTTGGGTTCT AATCGGGCCT CCGGGGTCCC TGACAGGTTC
AGTGGCAGTG GATCAGGCAC AGATTTTACA CTGAAAATCA GCAGAGTGGA GGCTGAGGAT GTTGGGGTTT
ATTACTGCAT GCAAGCTCTA CAAACTCCTC TTACTTTCGG CGGAGGGACC AAGGTGGAGA TCAAA

L15 (SEQ ID NO:29)
 GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC
AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACT ATTTGGATTG GTACCTGCAA AAGCCAGGGC
AGTCTCCACA GCTCCTGATC TATTTGGGTT CTTATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGCCAG
TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAGG ATGTTGGGGT TTATTACTGC
ATGCAAGCTC TACAAACTCC GATCACCTTC GGCCAAGGGA CACGACTGGA GATTAAA

L16 (SEQ ID NO:31)
 GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC
AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC
AGTCTCCACA GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGGCAG
TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGGGTG GAGGCTGAGG ATGTTGGGGT TTATTACTGC
ATGCAAGGTA CACACTGGCC TCTGACGTTC GGCCAAGGGA CCAAGGTGGA GATCAAA

L17 (SEQ ID NO:33)
  GAAATTG TGATGACGCA GTCTCCACTC TCCCTGCCCG TCACCCCTGG AGAGCCGGCC TCCATCTCCT
GCAGGTCTAG TCAGAGCCTC CTGCATAGTA ATGGATACAA CTATTTGGAT TGGTACCTGC AGAAGCCAGG
GCAGTCTCCA CAGCTCCTGA TCTATTTGGG TTCTAATCGG GCCTCCGGGG TCCCTGACAG GTTCAGTGGC
AGTGGATCAG GCACAGATTT TACACTGAAA ATCAGCAGAG TGGAGGCTGA GGATGTTGGG GTTTATTACT
GCATGCAAGC TCTACAAACT CCTCTCACTT TCGGCGGAGG GACCAAGGTG GAGATCAAA

L18 (SEQ ID NO:35)
        GAC ATCCAGTTGA CCCAGTCTCC ATCTTCCGTG TCTGCGTCTG TCGGAGACAG AGTCACCATC
ACTTGTCGGG CGAGTCAGGG TATTAGCAGG TGGTTAGCCT GGTATCAACA GAAACCAGGG AAAGCCCCTA
GACTCCTGAT CTATGCTGCG TCCGGTTTAC AAAGTGGGGT CCCATCAAGG TTCAGCGGCA GTGGATCTGG
GACAGATTTC ACTCTCACCA TCAGCAACCT GCAGCCTGAA GATTTTGCAA CTTACTATTG TCAACAGGCT
AGCAGTTTTC CAATCACCTT CGGCCAAGGG ACACGACTGG AGACTAAA

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L19 (SEQ ID NO:37)
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      GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC
TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC
CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTCAG
TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGAGTTTAT
TACTGCATGC AAGCTCTACA AACTCCGTAC ACTTTTGGCC AGGGGACCAA GCTGGAGATC AAA
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L20 (SEQ ID NO:39)
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 GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC
AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC
AGTCTCCACA GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTAACAGGT TCAGTGGCAG
TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAGG ATGTTGGGGT TTATTACTGC
ATGCAAGCTC TACAAACTCC ATTCACTTTC GGCCCTGGGA CCAAAGTGGA TATCAAA
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L21 (SEQ ID NO:41)
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 GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC
AGGTCTAGTC AGAGCCTCCT GCATAGTCAT GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC
AGTCTCCACA ACTTCTGATC TATTTGGGTT CTTATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGGCAG
TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAGG ATGTTGGGGT TTATTACTGC
ATGCAATCTC TAGAAGTTCC GTTCACTTTT GGCCAGGGGA CCAAGCTGGA GATCAAA
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L22 (SEQ ID NO:43)
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      TCT TCTGAGCTGA CTCAGGACCC TGCTGTGTCT GTGGCCTTGG GACAGACAGT CAGGATCACA
TGCCAAGGAG ACAGCCTCAG AATTTATTAT ACAGGCTGGT ACCAACAGAA GCCAGGACAG GCCCCTGTGC
TTGTCCTCTT TGGTAAGAAC AATCGGCCCT CAGGGATCCC AGACCGATTC TCTGGCTCCC ACTCAGGGAA
CACAGCTTCC TTGACCATCA CTGGGGCTCA AGCGGAAGAT GAGGCTGACT ATTACTGTAA CTCCCGGGAC
ATCACTGGTG TCCATCGATT CGGCGGAGGG ACCAAGCTGA CCGTCCTA
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L23 (SEQ ID NO:45)
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      GAA ATTGTGCTGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC
TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC
CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTCAG
TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT
TACTGCATGC AAGCTCTACA AACTCCTCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA
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L24 (SEQ ID NO:47)
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      GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC
TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC
CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTCAG
TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT
TACTGCATGC AAGCTCTACA AACTCCTAAC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA
```

L25 (SEQ ID NO:49)
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 GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC
AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC
AGTCTCCACA GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGGCAG
TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAGG ATGTTGGGGT TTATTACTGC
ATGCAAGCTC TACAAACTCC AATCACTTTC GGCCCTGGGA CCAAAGTGGA TATCAAA
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L26 (SEQ ID NO:51)
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 GATGTTGT GATGACTCAG TCTCCACTCT CCCTGCCCGT CACCCCTGGA GAGCCGGCCT CCATCTCCTG
CAGGTCTAGT CAGAGCCTCC TGCATAGTAA TGGATACACC TATTTGGATT GGTACCTGCA GAAGCCAGGG
CAGTCTCCAC AACTCCTGAT CTATTTGGGT TCTAATCGGG CCTCCGGGGT CCCTGACAGG TTCAGCGGCA
GTGGATCAGG CACAGATTTT ACACTGAAAA TCAGCAGAGT GGAGCCTGAG GATGTTGGGG TCTATTACTG
CATGCAAGCT CTAGAAATGC CCCTCACTTT CGGCGGAGGG ACCAAGGTGG AGATCAAA
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L27 (SEQ ID NO:53)
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      GAC ATCCAGTTGA CCCAGTCTCC ATCCTTCCTG TCTGCATCTG TAGGAGACAG AGTCACCATC
ACTTGCCGGG CCAGTCAGGG CATTAGCAGT TATTTAGCCT GGTATCAGCA AAAACCAGGG AAAGCCCCTA
AGCTCCTGAT CTATGCTGCA TCCACTTTGC AAAGTGGGGT CCCATCAAGG TTCAGCGGCA GTGGATCTGG
GACAGAATTC ACTCTCACAA TCAGCAGCCT GCAGCCTGAA GATTTTGCAA CTTATTACTG TCAACAGCTT
AATAGTTACC CCCTCACTTT CGGCGGAGGG ACCAAGGTGG AGATCAAA
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L28 (SEQ ID NO:55)
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          TC CTATGTGCTG ACTCAGCCAC CCTCAGTGTC CGTGTCCCCA GGACAGACAG CCAGCATCAC
CTGCTCTGGA GATAAATTGG GGGATAAATA TGTTGGCTGG TATCAGCAAA AGGCAGGCCA AGCCCCTGTT
TTGGTCATCT ATCAAGACAA CAAGCGACCC TCAGGGATCC CTGAGCGATT CTCTGGCTCC AACTCTGGGA
ACACAGCCAG TCTGACCATC AGCGGGACCC AGGCTATGGA TGAGGCTGAC TATTACTGTC AGGCGTGGGA
CAGCGGCACG GTGTTCGGCG GAGGGACCAA GCTGACCGTC CTA
```

L29 (SEQ ID NO:57)
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        GATG TTGTGATGAC TCAGTCTCCA CTCTCCCTGC CCGTCACCCC TGGAGAGCCG GCCTCCATCT
CCTGCAGGTC TAGTCAGAGC CTCCTGCATA GTAATGGATA CAACTATTTG GATTGGTACC TGCAGAAGCC
AGGGCAGTCT CCACAGCTCC TGATCTATTT GGGTTCTAAT CGGGCCTCCG GGGTCCCTGA CAGGTTCAGT
GGCAGTGGAT CAGGCACAGA TTTTACACTG AAAATCAGCA GAGTGGAGGC TGAGGATGTT GGGGTTTATT
ACTGCATGCA AGCTCTACAA ACCCCCCTCA CTTTCGGCGG AGGGACCAAG GTGGAGATCA AA
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L30 (SEQ ID NO:59)
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GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC
AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC
AGTCTCCACA GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGGCAG
TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAGG ATGTTGGGGT TTATTACTGC
ATGGAAGCTC TACAAACTCC ATTCACTTTC GGCCCTGGGA CCAAGGTGGA AATCAAA
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L31 (SEQ ID NO:61)
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     GACATC CAGTTGACCC AGTCTCCATC CTCCCTGTCT GCGTCTGTGG GAGACAGAGT CACCATCACT
TGCCGGTCAA GTCAAGGCAT TGGTTACTTC TTAAATTGGT ATCAGCAGGA ACCAGGGAAA GCCCCAAAGA
TCCTGATCTC TGCTGCATCC ACTTTGCAAA GTGGGGTCCC ATCAAGGTTC AGTGGCAGTG GATCTGGGAC
AGATTTCACA CTCTCCATCA ACAATCTGCA ACCCGCAGAT TTTGCGACAT ACTACTGTCA ACAGAGTCAC
AGTCCCCCGT ACACTTTCGG CCAGGGGACC AAGGTGGAGA TCAAA
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L32 (SEQ ID NO:63)
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        GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC
TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC
CAGGGCAGTC TCCACAGCTC CTGATCTATT TGGGTTCTAA TCGGGCCTCC GGGGTCCCTG ACAGGTTCAG
TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT
TACTGCATGC AAGCTCTACA AACTCCGCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA
```

L33 (SEQ ID NO:65)
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GAAATTGTG CTGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC
AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC
AGTCTCCACA GCTCCTGATG TATTTGGTTT CTAATCGGGC CTCCGGGGTC CCTGAGAGGT TCAGTGGCAG
TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAGG ATGTTGGGGT TTATTACTGC
ATGCAAACTC TACAAACTCC TCTCAGTTTT GGCCAGGGGA CCAAGCTGGA GATCAAA
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L34 (SEQ ID NO:67)
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GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC
AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC
AGTCTCCACA GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGGCAG
TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGAGTG GAGGCTGAGG ATGTTGGGGT TTATTACTGC
ATGCAAGCTC TACAAACTCC GCTCACTTTC GGCGGAGGGA CCAAGGTGGA GATCAAA
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L35 (SEQ ID NO:69)
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AATTTTATG CTGACTCAGC CCCACTCTGT GTCGGCGTCT CCGGGGAAGA CGGTTACCAT CTCCTGCACC
CGCAGCAGTG GCGACATTGA CAACAACTAT GTGCAGTGGT ACCAGCAGCG CCCGGGCAAT TCCCCCACCA
ATGTGATTTA TGAGGATAAC CGAAGACCCT CTGGGGTCCC GGATCGCTTC TCTGGCTCCA TCGACAGCTC
CTCCAACTCT GCCTCCCTCA CCATCTCTGG ACTGCAGCCT GAGGACGAGG CTGACTACTA TTGTCAGTCT
TATCAAAGCG ACAATTGGGT GTTCGGCGGA GGGACCAAGG TGACCGTCCT A
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L36 (SEQ ID NO:71)
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AATTTTATG CTGACTCAGC CCCACTCTGT GTCGGAGTCT CCGGGGAAGA CGGTAACCAT CTCCTGCACC
CGCAGCAGTG GCAGCATTGC CAGCAACTAT GTGCAGTGGT ACCAGCAGCG CCCGGGCAGT TCCCCCACCA
CTGTGATCTA TGAGGATAAC CAAAGACCCT CTGGGGTCCC TGATCGATTC TCTGGCTCCA TCGACAGCTC
CTCCAACTCT GCCTCCCTCA CCATCTCTGG ACTGAAGACT GAGGACGAGG CTGACTACTA CTGTCAGTCT
TATGATAGCA GCAATGTGGT GTTCGGCGGA GGGACCAAGC TGACCGTCCT A
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L37 (SEQ ID NO:73)
GATGTTGTGA TGACTCAGTC TCCACTCTCC CTGCCCGTCA CCCCTGGGGA GCCGGCCTCC ATCTCCTGCA
GGTCTAGTCA GAGCCTCCTG CATAGTAATG GATACAACTA TTTGGATTGG TACCTGCAGA AGCCAGGGCA
GTCTCCACAG CTCCTGATCT ATTTGGGTTC TAACCGGGAC TCTGGGGTCC CAGACAGATT CAGCGGCAGT
GGGTCAGGCA CTGATTTCAC ACTGAAAATC AGCAGGGTGG AGGCTGAGGA TGTTGGGGTT TATTACTGCA
TGCAAGGTAC ACACTGGCCG TACACTTTTG GCCAGGGGAC CAGGCTGGAG ATCAAA

L38 (SEQ ID NO:75)
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CAGGTCTAGT CAGAGCCTCC TGCATAGTAA TGGATACAAC TTTTTGGATT GGTACCTGCA GAAGCCAGGG
CAGTCTCCAC AGCTCCTGAT CTATTTGGGT TCTAATCGGG CCTCCGGGGT CCCTGACAGG TTCAGTGGCA
GTGGATCAGG CACAGATTTT ACACTGAAAA TCAGCAGAGT GGAGGCTGAG GATGTTGGGG TTTATTACTG
CATGCAAGCT CTACAAACTC CTCTCACTTT CGGCGGAGGG ACCAAGGTGG AGATCAAA

L39 (SEQ ID NO:77)
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CTCCTGCAGG TCTAGTCAGA GCCTCCTGCA TAGTAATGGA TACAACTATT TGGATTGGTA CCTGCAGAAG
CCAGGGCAGT CTCCACAGCT CCTGATCTAT TTGGGTTCTA ATCGGGCCTC CGGGGTCCCT GACAGGTTCA
GTGGCAGTGG ATCAGGCACA GATTTTACAC TGAAAATCAG CAGAGTGGAG GCTGAGGATG TTGGGGTTTA
TTACTGCATG CAAGCTCTAC AAACCCCCCT CACTTTCGGC GGAGGGACCA AGGTGGAGAT CAAA

L40 (SEQ ID NO:79)
 GAAACGAC ACTCACGCAG TCTCCAGCCA CCCTGTCTTT GTCTCCAGGG CAAAGAGCCA CCCTCTCCTG
CAGGGCCAGT CAGAGTGTCT ACAACTACTT AGCCTGGTAC CAACAGAAGC CTGGCCAGGC TCCCAGGCTC
CTCATCTATG ATGCATCCAG AAGGGCAACT GGCATCCCAG CCAGGTTCAG TGGCAGTGGG TCTGGGACAG
ACTTCACTCT CACCATCAGC AGCCTAGAGC CTGAAGATTT TGCAGTTTAT TACTGTCAGC AGCGTAACAA
CTGGCCGCTC ACTTTCGGTG GAGGGACCAA GGTGGAGATC AAA

L41 (SEQ ID NO:81)
 GACAT CCAGTTGACC CAGTCTCCAT CCTCCCTGTC TGCTTCTGTT GGAGACAGCG TCACCATCTC
TTGCCGGGCA AGTCAGAGTC CTGGCATCTT TTTAAATTGG TATCAGCAGA TACCAGGGAA AGCCCCTAAA
CTCCTGATCT ACGCTACATC CACTCTGGAA AGTGGGGTCC CCCCCAGGTT CACCGGCAGT GGATCTGGGA
CAGATTTCAC TCTCACCATC AGCAGTCTGC AACCTGAGGA CTTTGCAACT TACTACTGTC AACAGAGTAA
CAGTGTTCCG CTCACTTTCG GCGGCGGGAC CAAGGTGGAG ATCAAA

L42 (SEQ ID NO:83)
  GATGT TGTGATGACT CAGTCTCCAC TCTCCCTGCC CGTCACCCCT GGAGAGCCGG CCTCCATCTC
CTGCAGGTCT AGTCAGAGCC TCCTGCATAG TAATGGATAC AACTATTTGG ATTGGTACCT GCAGAAGCCA
GGGCAGTCTC CACAGCTCCT GATCTATTTG GGTTCTAATC GGGCCTCCGG GGTCCCTGAC AGGTTCAGTG
GCAGTGGATC AGGCACAGAT TTTACACTAA AAATCAGCAG AGTGGAGGCT GAGGATGTTG GGGTTTATTA
CTGCATGCAA GCTCTACAAA CTCCTCTAAC CTTCGGCCAA GGGACACGAC TGGAGATTAA A

L43 (SEQ ID NO:85)
  GAAATT GTGATGACGC AGTCTCCAGC CACCCTGTCT GTGTCTCCAG GGGAAAGAGC CACCTTCTCC
TGTAGGGCCA GTCAGAGTGT TGGCAGCAAC TTAGCCTGGT ACCAGCAGAA ACCTGGCCAG GCTCCCAGGC
TCCTCATCTA TGATGCATCC AACAGGGCCA CTGGCATCCC AGCCAGGTTC AGTGGCAGTG GGTCTGGGAC
AGACTTCACT CTCACCATCA GCAGACTGGA GCCTGAAGAT TTTGCAGTGT ATTACTGTCA GCAGCGTAGC
AACTGGCCCC TCACTTTCGG CGGAGGGACC AAGGTGGAGA TCAAA

L44 (SEQ ID NO:87)
  GATGT TGTGATGACT CAGTCTCCAC TCTCCCTGCC CGTCACCCCT GGAGAGCCGG CCTCCATCTC
CTGCAGGTCT AGTCAGAGCC TCCTGCATAG TAATGGATAC AACTATTTGG ATTGGTACCT GCAGAAGCCA
GGGCAGTCTC CACAGCTCCT GATCTATTTG GGTTCTAATC GGGCCTCCGG GGTCCCTGAC AGGTTCAGTG
GCAGTGGATC AGGCACAGAT TTTACACTGA AAATCAGCAG AGTGGAGGCT GAGGATGTTG GGGTTTATTA
CTGCATGCAA GCTCTACAAA CTCCGCTCAC TTTCGGCGGA GGGACCAAGG TGGAGATCAA A

L45 (SEQ ID NO:89)
   GAT GTTGTGATGA CTCAGTCTCC ACTCTCCCTG CCCGTCACCC CTGGAGAGCC GGCCTCCATC
TCCTGCAGGT CTAGTCAGAG CCTCCTGCAT AGTAATGGAT ACAACTATTT GGATTGGTAC CTGCAGAAGC
CAGGGCAGTC TCCACAGCTC CTGATCTACT TGGGTTCTAC TCGGGCCTCC GGCGTCCCTG ACAGGTTCAG
TGGCAGTGGA TCAGGCACAG ATTTTACACT GAAAATCAGC AGAGTGGAGG CTGAGGATGT TGGGGTTTAT
TACTGCATGC AAGCTCTACA AACTCCTTAC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAA

L46 (SEQ ID NO:91)

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        GATGT TGTGATGACT CAGTCTCCAC TCTCCCTGCC CGTCACCCCT GGAGAGCCGG CCTCCATCTC
CTGCAGGTCT AGTCAGAGCC TCCTGCATAG TAATGGATAC AACTATTTGG ATTGGTACCT GCAGAAGCCA
GGGCAGTCTC CACAGCTCCT GATCTATTTG GGTTCTAATC GGGCCTCCGG GGTCCCTGAC AGGTTCAGTG
GCAGTGGATC AGGCACAGAT TTTACACTGA AAATCAGCAG AGTGGAGGCT GAGGATGTTG GGGTTTATTA
CTGCATGCAA GCTCTACAAA CTCCCCTCAC TTTCGGCGGA GGGACCAAGG TGGAGATCAA A
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L47 (SEQ ID NO:93)
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        GATGT TGTGATGACT CAGTCTCCAC TCTCCCTGCC CGTCACCCCT GGAGAGCCGG CCTCCATCTC
CTGCAGGTCT AGTCAGAGCC TCCTGCATAC TAATGGATAC AACTATTTGG ATTGGTACCT GCAGAAGCCA
GGGCAGTCTC CACGGCTCCT GATCTATTTG GGTTTTAATC GGGCCTCCGG GGTCCCTGAC AGGTTCAGTG
GCAGTGGATC AGGCACAGAT TTTACACTGA AAATCAGCAG AGTGGAGGCT GAGGATGTTG GGGTTTATTA
CTGTATGCAA GGTCTACAAA CTCCCCTCAC TTTCGGCGGA GGGACCAAGG TGGAGATCAA A
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L48 (SEQ ID NO:95)
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 GATGTTGTG ATGACTCAGT CTCCACTCTC CCTGCCCGTC ACCCCTGGAG AGCCGGCCTC CATCTCCTGC
AGGTCTAGTC AGAGCCTCCT GCATAGTAAT GGATACAACT ATTTGGATTG GTACCTGCAG AAGCCAGGGC
AGTCTCCACA GCTCCTGATC TATTTGGGTT CTAATCGGGC CTCCGGGGTC CCTGACAGGT TCAGTGGCAG
TGGATCAGGC ACAGATTTTA CACTGAAAAT CAGCAGGGTG GAGGCTGAGG ATGTTGGGGT TTATTATTGC
ATGCAAGCTA CACACTGGCC GTACACTTTT GGCCAGGGGA CCAAGCTGGA GATCAAA
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L49(SEQ ID NO:97)
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   AATTTTA TGCTGACTCA GCCCCACTCT GTGTCGGAGT CTCCGGGGAA GACGGTAAGC ATCTCCTGCA
CCCGCAACAG TGGCAGCATT GCCAGCAACT TTGTGCAGTG GTACCAGCAG CGCCCGGGCA GTGCCCCCAC
CATTGTAATC TATGAGGATA ACCAAAGACC CTCTGCGGTC CCTACTCGGT TCTCTGGCTC CATCGACAGG
TCCTCCAACT CTGCCTCCCT CACCATCTCT GGACTGACGA CTGAGGACGA GGCTGACTAC TACTGTCAGT
CTTATGATAG CGCCAATGTC ATTTTCGGCG GGGGGACCAA GCTGACCGTC CTA
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L50 (SEQ ID NO:99)
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    GAAACG ACACTCACGC AGTCTCCAGG CACCCTGTCT TTGTCTCCAG GGGAGAGAGC CACCCTCTCC
TGCAGGGCCA GTCAGACTAT CAGCAGCAGC CACTTAGCCT GGTACCAGCA GAAACCTGGC CAGTCTCCCA
GGCTCCTCAT CTATGGTGCG GGCTACAGGG CCACCGGCAT TCCAGACAGG TTCAGTGGCA GTGGGTCTGG
CACAGACTTC ACTCTCACCA TCAGCAGACT GGAGCCTGAA GATTTTGCAG TGTATTACTG TCAGCACTAT
GGTAGTTCAC TCCGGACGTT CGGCCAAGGG ACCAAGGTGG AAATCAAA
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L51 (SEQ ID NO:101)
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    AATTTT ATGCTGACTC AGCCCCACTC TGTGTCGGAG TCTCCGGGGA AGACGGTAAC CATCTCCTGC
ACCGGCAGCG GTGGCAACAT TGCCAGCAAT TATGTGCAGT GGTACCAGCA GCGCCCGGGC AGGGCCCCCA
CCACTGTGAT CTATGAGGAT AATCGAAGAC CCTCTGGGGT CCCTGATCGG TTCTCTGGCT CCATCGACAG
CTCCTCCAAC TCTGCCTCCC TCACCATCTC TGGACTGAAG ACTGAAGACG AGGCTGACTA CTACTGTCAG
TCTTATGATC CCTACAATCG AGTGTTCGGC GGAGGGACCA AGCTGACCGT CCTA
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L51 (SEQ ID NO:103)
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       GAAA TTGTGATGAC GCAGTCTCCA CTCTCCCTGC CCGTCACCCC TGGAGAGCCG GCCTCCATCT
CCTGCAGGTC TAGTCAGAGC CTCCTGCATA CTAATGGATA CGACTATTTG GATTGGTACC TGCAGAAGCC
AGGGCAGTCT CCACAGCTTC TGATCTATTT GGGTTCTACT CGGGCCTCCG GGGTCCCTGA CAGGTTCAGT
GGCAGTGGAT CGGGCACAGA TTTTACACTG AAAATCAGCA GAGTGGAGGC TGAGGATGTT GGGGTTTATT
ACTGCATGCA AGCTTTTCAA ACTCCGCTCA CTTTCGGCGG AGGGACCAAG ATGGAGATCA AA
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H1 (SEQ ID NO:105)
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GAGGTGCAGC TGGTGGAGAC CGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC ACCTGCGCTG
TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT
ATTACTGTGC GAGATTTAAT TACTATGATA GTAGTGTCTG GGGCCAGGGA ACCCTGGTCA CCGTCTCAAG
C
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H2 (SEQ ID NO:107)
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GAGGTGCAGC TGGTGGAGAC CGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC ACCTGCGCTG
TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT
ATTACTGTGC GAGAGGGGTT GAGCAGATTG ACTACTGGGG CCAGGGAACC CTGGTCACCG TCTCAAGC
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H3 (SEQ ID NO:109)
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CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC ACCTGCGCTG
TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA
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TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC TGCCGCGGAC ACGGCCGTGT
ATTACTGTGC GAAAAATTTA GCAGCAGGGG CGGTTGCCTA CTGGGGCCAG GGCACCCTGG TCACCGTCTC
AAGC

H4 (SEQ ID NO:111)

 CAGGTGCAG CTACAGCAGT GGGGCGCAGG ACTGTTGAAG CCTTCGGAGA CCCTGTCCCT CACCTGCGCT
GTCTCTGGTG GGTCCTTCAG TGGTTACTAC TGGAGCTGGA TCCGTCAGCC CCCAGGGAAG GGGCTGGAGT
GGATTGGGGA AATCAATCAT AGTGGAAGTA CCAACTACAA CCGGTCCCTC AAGAGTCGAG TCACCATATC
AGTAGACACG TCCAAGAACC AGTTCTCCCT GAAGCTGAGC TCTGTGACCG CCGCGGACAC GGCTGTGTAT
TACTGTGCGA GACTTTCATA TGGTTCGGGC GTTGACTACT GGGGCCAGGG CACCCTGGTC ACCGTCTCAA
GC

H5 (SEQ ID NO:113)

         C AGCTGCAGCT GCAGGAGTCG GGCCCAGGAC TGGTGAAGCC TTCACAGACC CTGTCCCTCA
CCTGCACTGT CTCTGGTGGC TCCATCAGCA GTAGTAACTG GTGGAGTTGG GTCCGCCAGC CCCCAGGGAA
GGGGCTGGAG TGGATTGGGG AAATCTATCA TAGTGGGAGC ACCAACTACA ACCCGTCCCT CAAGAGTCGA
GTCACCATAT CAGTAGACAA GTCCAAGAAC CAGTTCTCCC TGAAGCTGAG CTCTGTGACC GCCGCGGACA
CGGCCGTGTA TTACTGTGCG AGGTATAGCA GCAGCCGCAA TGATGCTTTT GATATCTGGG GCCAAGGGAC
AATGGTCACC GTCTCAAGC

H6 (SEQ ID NO:115)

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC ACCTGCGCTG
TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT
ATTACTGTGC GAGAGATGGG CAGCTGGATG CTTTTGATAT CTGGGGCCAA GGGACAATGG TCACCGTCTC
AAGC

H7 (SEQ ID NO:117)

CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC ACCTGCGCTG
TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT
ATTACTGTGC GAGATTTTGG GACTACTACG GTATGGACGT CTGGGGCCAA GGGACCACGG TCACCGTCTC
AAGC

H8 (SEQ ID NO:119)

   CAGGTG CAGCTACAGC AGTGGGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC
GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC
TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCGAGA GTCGAGTCAC
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCGC AGACACGGCC
GTGTATTACT GTGCGAGAGA TCGGTACTAC GGTATGGACG TCTGGGGCCA AGGGACCACG GTCACCGTCT
CAAGC

H9 (SEQ ID NO:121)

        G AGGTGCAGCT GGTCGAGTCT GGCCCAGGAC TGGTGAAGCC TTCGGGGACC CTGTCCCTCA
CCTGCGCTGT CTCTGGTGGC TCCATCAGCA GTAGTAACTG GTGGAGTTGG GTCCGCCAGC CCCCAGGGAA
GGGGCTGGAG TGGATTGGGT ACATCTATTA TAGTGGGAGC ACCTACTACA ACCCGTCCCT CAAGAGTCGA
GTCACCATGT CAGTAGACAC GTCCAAGAAC CAGTTCTCCC TGAAGCTGAG CTCTGTGACC GCCGCAGACA
CGGCCGTGTA TTACTGTGCG AGATGGAGCT ACTTGGATGC TTTTGATATC TGGGGCCAAG GGACAATGGT
CACCGTCTCA AGC

H10 (SEQ ID NO:123)

   GAGGTGC AGCTGGTGGA GTCTGGCCCA GGACTGGTGA AGCCTTCGGG GACCCTGTCC CTCACCTGCG
CTGTCTCTGG TGGCTCCATC AGCAGTAGTA ACTGGTGGAG TTGGGTCCGC CAGCCCCCAG GGAAGGGGCT
GGAGTGGATT GGGGAAATCT ATCATAGTGG GAGCACCAAC TACAACCCGT CCCTCAAGAG TCGAGTCACC
ATATCAGTAG ACAAGTCCAA GAACCAGTTC TCCCTGAAGC TGAGCTCTGT GACCGCCGCG GACACGGCCG
TGTATTACTG TGCGAGAGAT TACGATATTT TCGGTATGGA CGTCTGGGGC CAAGGGACCA CGGTCACCGT
CTCAAGC

H11 (SEQ ID NO:125)

      CAGCT GCAGCTGCAG GAGTCGGGCC CAGGACTGGT GAAGCCTTCG GGGACCCTGT CCCTCACCTG
CGCTGTCTCT GGTGGCTCCA TCAGCAGTAG TAACTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG
CTGGAGTGGA TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC GTCCCTCAAG AGTCGAGTCA
CCATATCAGT AGACAAGTCC AAGAACCAGT CCTCCCTGAA GCTGAGCTCT GTGACCGCCG CGGACACGGC

CGTGTATTAC TGTGCGAGAG CCAACAGAGA TGATGCTTTT GATATCTGGG GCCAAGGGAC AATGGTCACC
GTCTCAAGC

H12 (SEQ ID NO:127)
GAGGTGC AGCTGGTGGA GTCTGGGGGA GGCTTGGTAC AGCCGGGGGG GTCCCTGAGA CTCTCCTGTG
CAGCCTCTGG ATTCACCTTT AGCAGCTATG CCATGAGCTG GGTCCGCCAG GCTCCAGGGA AGGGGCTGGA
GTGGGTCTCA GCTATTAGTG GTAGTGGTGG TAGCACATAC TACGCAGACT CCGTGAAGGG CCGGTTCACC
ATCTCCAGAG ACAATTCCAA GAACACGCTG TATCTGCAAA TGAACAGTCT GAGCGCCGAC GACACGGCCG
TATATTTCTG TGCGTCGGGT GGCTGGTACG GGGACTACTT TGACTACTGG GGCCAGGGAA CCCTGGTCAC
CGTCTCAAGC

H13 (SEQ ID NO:129)
CAGGTGCAGC TGCAGGAGTC CGGCCCAGGA CTGGTGAAGC CTTCGGAGAC CCTGTCCCTC ACCTGCACTG
TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT
ATTACTGTGC GAGAGAAGGG AACCGAACGG TGACTAGTGC TTTTGATATC TGGGGCCAAG GGACAATGGT
CACCGTCTCA AGC

H14 (SEQ ID NO:131)
CAGGTGCA GCTGCAGGAG TCCGGCCCAG GACTGGTGAA GCCTTCGGGG ACCCTGTCCC TCACCTGCGC
TGTCTCTGGT GGCTCCATCA GCAGTAGTAA CTGGTGGAGT TGGGTCCGCC AGCCCCCAGG GAAGGGGCTG
GAGTGGATTG GGGAAATCTA TCATAGTGGG AGCACCAACT ACAACCCGTC CCTCAAGAGT CGAGTCACCA
TATCAGTAGA CAAGTCCAAG AACCAGTTCT CCCTGAAGCT GAGCTCTGTG ACCGCTGCGG ACACGGCCGT
GTACTACTGT GCGAGAGGGC TGGGGGATAG TAGTGGTTAT ATCCTTTGGG GCCAAGGGAC AATGGTCACC
GTCTCAAGC

H15 (SEQ ID NO:133)
CAGGTG CAGCTGCAGG AGTCCGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC
GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC
TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCTGC GGACACGGCC
GTGTACTACT GTGCGAGAGG GCTGGGGGAT AGTAGTGGTT ATATCCTTTG GGGCCAAGGG ACAATGGTCA
CCGTCTCAAG C

H16 (SEQ ID NO:135)
CAGGTG CAGCTGCAGG AGTCGGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC
GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC
TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCGC GGACACGGCC
GTGTATTACT GTGCGAGATG GACCGGGCGT ACTGATGCTT TTGATATCTG GGGCCAAGGG ACAATGGTCA
CCGTCTCAAG C

H17 (SEQ ID NO:137)
CAGG TGCAGCTGCA GGAGTCCGGC CCAGGACTGG TGAAGCCTTC GGGGACCCTG TCCCTCACCT
GCGCTGTCTC TGGTGGCTCC ATCAGCAGTA GTAACTGGTG GAGTTGGGTC CGCCAGCCCC CAGGGAAGGG
GCTGGAGTGG ATTGGGGAAA TCTATCATAG TGGGAGCACC AACTACAACC CGTCCCTCAA GAGTCGAGTC
ACCATATCAG TAGACAAGTC CAAGAACCAG TTCTCCCTGA AGCTGAGCTC TGTGACCGCC GCGGACACGG
CCGTGTATTA CTGTGCGAGA CAAGGGGCGT TAGATGCTTT TGATATCTGG GGCCAAGGGA CCACGGTCAC
CGTCTCAAGC

H18 (SEQ ID NO:139)
GCAGCTGGTG GAGTCCGGGG GAGGCGTGGT CCGACCTGGG GGGTCCCTGA GACTCTCCTG TGCAGCGTCT
GGATTCACCT TTAGCAGCTA TGCCATGAGC TGGGTCCGCC AGGCTCCAGG GAAGGGGCTG GAGTGGGTCT
CAACTATTAG TGGTAGTGGT GGTAGCACAT ACTACGCAGA CTCCGTGAAG GGCCGGTTCA CCATCTCCAG
AGACAATTCC AAGAACACGC TGTATCTGCA GATGAACAGC CTGAGAGCCG AGGACACGGC CGTATATTAC
TGTGCGAAAG AGCGTGGCAG TGGCTGGTCC TTAGACAATA TGGACGTCTG GGGCCAAGGG ACCACGGTCA
CCGTCTCAAG C

H19 (SEQ ID NO:141)
CAGGTGCAGC TGGTGGAGTC TGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC ACCTGCGCTG
TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCTGCGGAC ACGGCCGTGT
ATTACTGTGC GAGAGATAGC AGTGGGTTCT ACGGTATGGA CGTCTGGGGC CAAGGGACCA CGGTCACCGT
CTCAAGC

H20 (SEQ ID NO:143)
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      CAGGTG CAGCTGCAGG AGTCGGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC
GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC
TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACTGCCGC GGACACGGCC
GTGTATTACT GTGCGAGAAG CAGCAGCTGG TACTGGAATG CTTTTGATAT CTGGGGCCAA GGGACAATGG
TCACCGTCTC AAGC
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H21 (SEQ ID NO:145)
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      CAGGTG CAGCTACAGC AGTGGGGCCC AGCACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC
TCTGTCTCTG GTGTCTCCAT CACCAGTAAT ATCTGGTGGA GTTGGGTCCG CCAGTCCCCA GGGAAGGGGC
TGGAGTGGAT TGGGGAAGTC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCGC GGACACGGCT
GTGTATTACT GTGCGGGGTA CCGTAGCTTC GGGGAGTCCT ACTGGGGCCA GGGAACCCTG GTCACCGTCT
CAAGC
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H22 (SEQ ID NO:147)
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    CAGGTGCA GCTACAGCAG TGGGGCGCAG GGCTGTTGAA GCCTTCGGAG ACCCTGTCTC TCACCTGCGT
TGTCTATGGT GGGTCCTTCA GCGATTTCTA CTGGAGCTGG ATCCGCCAGC CCCCAGGGAA GGGGCCAGAG
TGGATTGGGG AAGTCAATCC TAGAGGAAGC ACCAACTACA ACCCGTCCCT CAAGAGTCGA GCCACCATAT
CACTAGACAC GTCCAAGAAC ĊAGTTCTCCC TGAAGCTGAG TTCTGTGACC GCCGCGGACA CGGCTGTGTA
TTTCTGTGCG AGAGGTCCTC GGCCCGGGAG AGATGGCTAC AATTACTTTG ACAACTGGGG CCAGGGCACC
CTGGTCACCG TCTCAAGC
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H23 (SEQ ID NO:149)
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CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC CCTGTCCCTC ACCTGCACTG
TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT
ATTACTGTGC GAGAGGTATA GCAGCAGCTG GTCAAGGTGA CTACTGGGGC CAGGGAACCC TGGTCACCGT
CTCAAGC
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H24 (SEQ ID NO:151)
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CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGAGAC CCTGTCCCTC ACCTGCACTG
TCTCTGGTGG CTCCATCAGC AGTAGTAGTT ACTACTGGGG CTGGATCCGC CAGCCCCCAG GGAAGGGGCT
GGAGTGGATT GGGAGTATCT ATTATAGTGG GAGCACCTAC TACAACCCGT CCCTCAAGAG TCGAGTCACC
ATATCCGTAG ACACGTCCAA GAACCAGTTC TCCCTGAAGC TGAGCTCTGT GACCGCCGCG GACACGGCCG
TGTATTACTG TGCGAGAGAT GGGGGATACT ACTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT
CACCGTCTCA AGC
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H25 (SEQ ID NO:153)
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      CAGGTG CAGCTGCAGG AGTCGGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC
GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC
TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCGC GGACACGGCC
GTGTATTACT GTGCGAGTAG TGGTTATGAT GCTTTTGATA TCTGGGGCCA AGGGACCACG GTCACCGTCT
CAAGC
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H26 (SEQ ID NO:155)
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       CAGGT GCAGCTGCAG GAGTCGGGCC CAGGACTGGT GAAGCCTTCG GGGACCCTGT CCCTCACCTG
CGCTGTCTCT GGTGGCTCCA TCAGCAGTAG TAATTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG
CTGGAGTGGA TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC GTCCCTCAAG AGTCGAGTCA
CCATATCAGT AGACAAGTCC AAGAACCAGT TCTCCCTGAA GCTGAGCTCT GTGACCGCCG CGGACACGGC
CGTGTATTAC TGTGCACGAT ACAGCTATGG AACGGTAGGA ATTGACTACT GGGGCCAGGG AACCCTGGTC
ACCGTCTCAA GC
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H27 (SEQ ID NO:157)
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       GAGGT GCAGCTGGTG CAGTCTGGGG GAGGCGTGGT CCAGCCTGGG ACGTCCCTGA GACTCTCCTG
TGCAGCCTCT GGATTCAGCT TCAGAAGTCA TGGCATGCAC TGGGTCCGCC AGGCTCCAGG CAAGGGGCTG
GAGTGGGTGG CAGTTATATC ATATGATGGA AGTAATAAAT ACTATGCAGA CTCCGTGAAG GGCCGATTCA
CCATCTCCAG AGACAATTCC AAGAACACGC TGTATCTGCA AATGAACAGC CTGAGAGCTG AGGACACGGC
TGTGTATTAC TGTGCGACTA TAGGGCCGGG GGGATTTGAC TACTGGGGCC AGGGCACCCT GGTCACCGTC
TCAAGC
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H28 (SEQ ID NO:159)
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        CAG GTGCAGCTGC AGGAGTCCGG CCCAGGACTG GTGAAGCCTT CGGAGACCCT GTCCCTCACC
TGCACTGTCT CTGGTGGCTC CATTAGAAAT TACTACTGGA GTTGGATCCG GCAGCCCCCA GGGAAGGGAC
TGGAGTGGAT TGGGTATATT TCTGACAGTG GGAATACCAA CTACAATCCC TCCCTCAAGA GTCGAGTCAC
CATATCAGTA GACACGTCCA AGAACCAGTT CTCCCTAAAG CTGACCTCTG TGACCGCCAC AGACACGGCT
GCGTATTTCT GTGCGAGACA TCGAAGCAGC TGGGCATGGT ACTTCGATCT CTGGGGCCGT GGCACCCTGG
TCACCGTCTC AAGC
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H29 (SEQ ID NO:161)
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          C AGGTGCAGCT GCAGGAGTCG GGCCCAGGAC TGGTGAAGCC TTCGGAGACC CTGTCCCTCA
CCTGCGCTGT CTCTGGTGGC TCCATCAGCA GTAGTAACTG GTGGAGTTGG GTCCGCCAGC CCCCAGGGAA
GGGGCTGGAG TGGATTGGGG AAATCTATCA TAGTGGGAGC ACCAACTACA ACCCGTCCCT CAAGAGTCGA
GTCACCATAT CAGTAGACAA GTCCAAGAAC CAGTTCTCCC TGAAGCTGAG CTCTGTGACC GCCGCGGACA
CGGCCGTGTA TTACTGTGCG AGAGTGGGCA GTGGCTGGTA CGTTGACTAC TGGGGCCAGG GAACCCTGGT
CACCGTCTCA AGC
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H30 (SEQ ID NO:163)
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      CAGGTG CAGCTGCAGG AGTCCGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC
GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC
TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCGC GGACACGGCC
GTGTATTACT GTGCGAGAGT TTCTGGCTAC TACTACTACG GTATGGACGT CTGGGGCCAA GGGACCACGG
TCACCGTCTC AAGC
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H31 (SEQ ID NO:165)
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    GAGGTCCA GCTGGTACAG TCTGGGGGAG GCGTGGTCCA GCCTGGGAGG TCCCTGAGAC TCTCCTGTGC
AGCCTCTGGA TTCACCTTCA GTAGCTATGG CATGCACTGG GTCCGCCAGG CTCCAGGCAA GGGGCTGGAG
TGGGTGGCAG TTATATCATA TGATGGAAGT AATAAATACT ATGCAGACTC CGTGAAGGGC CGATTCACCA
TCTCCAGAGA CAATTCCAAG AACACGCTGT ATCTGCAAAT GAACAGCCTG AGAGCTGAGG ACACGGCTGT
GTATTACTGT GCGAAAGCGT ATAGCAGTGG CTGGTACGAC TACTACGGTA TGGACGTCTG GGGCCAAGGG
ACCACGGTCA CCGTCTCAAG C
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H32 (SEQ ID NO:167)
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CAGGTGCAGC TGCAGGAGTC GGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC ACCTGCGCTG
TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT
ATTACTGTGC GAGAGCCAGC GTTGATGCTT TTGATATCTG GGGCCAAGGG ACAATGGTCA CCGTCTCAAG
C
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H33 (SEQ ID NO:169)
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      CAGGTG CAGCTGCAGG AGTCCGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC
GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC
TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCTGC GGACACGGCC
GTGTACTACT GTGCGAGAGG GCTGGGGGAT AGTAGTGGTT ATATCCTTTG GGGCCAAGGG ACAATGGTCA
CCGTCTCAAG C
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H34 (SEQ ID NO:171)
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      CAGGTA CAGCTGCAGC AGTCAGGCCC AGGACTGGTG AAGCCTTCGG GGACCCTGTC CCTCACCTGC
GCTGTCTCTG GTGGCTCCAT CAGCAGTAGT AACTGGTGGA GTTGGGTCCG CCAGCCCCCA GGGAAGGGGC
TGGAGTGGAT TGGGGAAATC TATCATAGTG GGAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC
CATATCAGTA GACAAGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACTCCCGA GGACACGGCT
GTGTATTACT GTGCAAGAGA TCACGGCCCC TTTGACTACT GGGGCCGGGG AACCCTGGTC ACCGTCTCAA
GC
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H35 (SEQ ID NO:173)
```
      CAGGT GCAGCTGGTG CAATCTGGGG GAGGCGTGGT CCAGCCTGGG AGGTCCCTGA GACTCTCCTG
TGCAGCCTCT GGATTCGCCT TCAGTAGCTA TGGCATGCAC TGGGTCCGCC AGGCTCCAGG GAAGGGGCTG
GAGTGGGTTT CATACATTAG TAGTAGTAGT AGTACCATAT ACTACGCAGA CTCTGTGAAG GGCCGATTCA
CCATCTCCAG AGACAATTCC AAGAACACGC TGTATCTGCA AATGAACAGC CTGAGAGCCG AGGACACGGC
TGTGTATTAC TGTGCGAGAG ATCGATTTGG TCGGGGCAC TTGCCCGACT ACTGGGGCCA GGGAACCCTG
GTCACCGTCT CAAGC
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H36 (SEQ ID NO:175)
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     CAGGT GCAGCTACAG CAGTGGGGCG CAGGACTGTT GAAGCCTTCG GAGACCCTGT CCCTCACCTG
CGCTGTCTAT GGTGGGTCCT TCAGTGGTTA CTACTGGAGC TGGATCCGCC AGCCCCCAGG GAAGGGGCTG
GAGTGGATTG GGGAAATCAA TCATAGTGGA AGCACCAACT ACAACCCGTC CCTCAAGAGT CGAGTCACCA
TATCAGTAGA CACGTCCAAG AACCAGTTCT CCCTGAAGCT GAGCTCTGTG ACCGCCGCGG ACACGGCTGT
GTATTACTGT GCGAGAGTTG GGTATAGCAG TGGCCGTGAC GTTGACTACT GGGGCCAGGG CACCCTGGTC
ACCGTCTCAA GC
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H37 (SEQ ID NO:177)
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   GAGGTCC AGCTGGTGGA GTCTGGCCCA GGACTGGTGA AGCCTTCGGG GACCCTGTCC CTCACCTGCG
CTGTCTCTGG TGGCTCCATC AGCAGTAGTA ACTGGTGGAG TTGGATCCGG CAGCCCCCAG GGAAGGGGCT
GGAGTGGATT GGGGAAATCT ATCATAGTGG GAGCACCAAC TACAACCCGT CCCTCAAGAG TCGAGTCACC
ATATCAGTAG ACAAGTCCAA GAACCAGTTC TCCCTGAAGC TGAGCTCTGT GACCGCCGCG GACACGGCCG
TGTATTACTG TGCGAGAGAT AGCAGCAGCT GGTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT
CACCGTCTCA AGC
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H38 (SEQ ID NO:179)
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    GAGGT CCAGCTGGTG GAGTCCGGCC CAGGACTGGT GAAGCCTTCG GAGACCCTGT CCCTCACCTG
CGCTGTCTCT GGTGGCTCCA TCAGCAGTAG TAACTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG
CTGGAGTGGA TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC GTCCCTCAAG AGTCGAGTCA
CCATATCAGT AGACAAGTCC AAGAACCAGT TCTCCCTGAA GCTGAGCTCT GTGACCGCTG CGGACACGGC
CGTATATTAT TGTGCGAGAT CGACGTGGTC CCTTGACTAC TGGGGCCAGG GCACCCTGGT CACCGTCTCA
AGC
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H39 (SEQ ID NO:181)
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  GAGGTCCAG CTGGTGGAGT CTGGCCCAGG ACTGGTGAAG CCTTCGGGGA CCCTGTCCCT CACCTGCGCT
GTCTCTGGTG GCTCCATCAG CAGTAGTAAC TGGTGGAGTT GGGTCCGCCA GCCCCCAGGG AAGGGGCTGG
AGTGGATTGG GGAAATCTAT CATAGTGGGA GCACCAACTA CAACCCGTCC CTCAAGAGTC GAGTCACCAT
ATCAGTAGAC AAGTCCAAGA ACCAGTTCTC CCTGAAGCTG AGCTCTGTGA CCGCTGCGGA CACGGCCGTA
TATTACTGTG CGAGACTCTC GTTTGCCGAT CCTTTTGATA TCTGGGGCCA AGGGACAATG GTCACCGTCT
CAAGC
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H40 (SEQ ID NO:183)
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CAGGTCCAGC TGGTGCAGTC TGGGGCTGAG GTGAAGAAGC CTGGGTCCTC GGTGAAGGTC TCCTGCAAGG
CTTCTGGAGG CACCTTCAGC AGCTATGCTA TCAGCTGGGT GCGACAGGCC CCTGGACAAG GGCTTGAGTG
GATGGGAAGG ATCATCCCCA TCCTTGGTAT AGCAAACTAC GCACAGAAGT TCCAGGGCAG AGTCACGATT
ACCGCGGACA AATCCACGAG CACAGCCTAC ATGGAGCTGA GCAGCCTGAG ATCTGAGGAC ACGGCCGTGT
ATTACTGTGC ATATGGTTCG GGGAGTTATT ACGACTACTA CTACATGGAC GTCTGGGGCA AAGGGACCAC
GGTCACCGTC TCAAGC
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H41 (SEQ ID NO:185)
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   GAGGTCC AGCTGGTGCA GTCTGGGGGA GGCTTGGTCC AGCCTGGGGG GTCCCTGAGA CTCTCCTGTT
CAGCCTCCGG ATTCACCTTC AGTAGCTATG CTATGCACTG GGTCCGCCAG GCTCCAGGGA AGGGACTGGA
ATATGTTTCA ACTATTAGTA GTAATGGGGA TAGCACATAC TACGCAGACT CCGTGAAGGG CAGATTCACC
ATCTCCAGAG ACAATTCCAA GAACACGCTG TATCTGCAAA TGAACAGCCT GAGAGCTGAG GACACGGCTG
TGTATTACTG TGCGAAAGAA GAAGTATGGC TACAGGCTTT TGATATCTGG GGCCAAGGGA CAATGGTCAC
CGTCTCAAGC
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H42 (SEQ ID NO:187)
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        CA GCTGCAGCTG CAGGAGTCGG GCCCAGGACT GGTGAAGCCT TCGGAGACCC TGTCCCTCAC
CTGCACTGTC TCTGGTGGCT CCATCAGTAG TAACTGGTGG AGTTGGGTCC GCCAGCCCCC AGGGAAGGGG
CTGGAGTGGA TTGGGGAAAT CTATCATAGT GGGAGCACCA ACTACAACCC CTCCCTCAAG AGTCGAGTCA
CCATCTCAGT AGACACGTCC AAGAACCAGT TCTCCCTGAA GCTGAGCTCT GTGACCGCTG CGGACACGGC
CGTGTATTAC TGTGCGAGAG ATAAGGGATA CATGGACGTC TGGGGCAAAG GGACCACGGT CACCGTCTCA
AGC
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H43 (SEQ ID NO:189)
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   CAGGTACA GCTGCAGCAG TCAGGGGCTG AGGTGAAGAA GCCTGGGTCC TCGGTGAAGG TCTCCTGCAA
GGCTTCTGGA GGCACCTTCA GCAGCTATGC TATCAGCTGG GTGCGACAGG CCCCTGGACA AGGGCTTGAG
TGGATGGGAA GGATCATCCC TATCCTTGGT ATAGCAAACT ACGCACAGAA GTTCCAGGGC AGAGTCACGA
TTACCGCGGA CAAATCCACG AGCACAGCCT ACATGGAGCT GAGCAGCCTG AGATCTGAGG ACACGGCCGT
GTATTACTGT GCGAGAGATC ATAGGTTCGA CTACGCCTGG TACTTCGATC TCTGGGGCCG TGGCACCCTG
GTCACCGTCT CAAGC
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H44 (SEQ ID NO:191)
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        CA GGTGCAGCTG CAGGAGTCGG GCCCAGGACT GCTGAAGCCT TCGGGGACCC TGTCCCTCAC
CTGCGCTGTC TCTGGTGGCT CCATCAGCAG TAGCAACTGG TGGAGTTGGG TCCGCCAGCC CCCAGGGGAG
GGGCTGGAGT GGATTGGGGA AATCTATCAT AGTGGGAGCA CCAACTACAA CCCGTCCCTC AAGAGTCGAG
TCACCATATC AGTAGACAAG TCCAAGAACC AGTTCTCCCT GAAGCTGAGC TCTGTGACCG CCGCGGACAC
GGCCGTCTAT TACTGTGCGA GAGATCTAAC GGGGAGTCTT GACTACTGGG GCCAGGGAAC CCTGGTCACC
GTCTCAAGC
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H45 (SEQ ID NO:193)
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CAGGTGCAGC TGCAGGAGTC CGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC ACCTGCGCTG
TCTCTGGTGG CTCCATCAGC AGTAGTAACT GGTGGAGTTG GGTCCGCCAG CCCCCAGGGA AGGGGCTGGA
GTGGATTGGG GAAATCTATC ATAGTGGGAG CACCAACTAC AACCCGTCCC TCAAGAGTCG AGTCACCATA
TCAGTAGACA AGTCCAAGAA CCAGTTCTCC CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT
ATTACTGTGC GAGAATACGC TATGATGCTT TTGATATCTG GGGCCAAGGG ACAATGGTCA CCGTCTCAAG
C
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H46 (SEQ ID NO:195)
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        CA GGTGCAGCTG CAGGAGTCGG GCCCAGGACT GGTGAAGCCT TCGGAGACCC TGTCCCTCAC
CTGCGCTGTC TCTGGTGGCT CCATCAGCAG TAGTAACTGG TGGAGTTGGG TCCGCCAGCC CCCAGGGAAG
GGGCTGGAGT GGATTGGGGA AATCTATCAT AGTGGGAGCA CCAACTACAA CCCGTCCCTC AAGAGTCGAG
TCACCATATC AGTAGACAAG TCCAAGAACC AGTTCTCCCT GAAGCTGAGC TCTGTGACCG CTGCGGACAC
GGCCGTGTAT TACTGTGCCG TGACGGCAGC CCATGATGCT TTTGATATCT GGGGCCAAGG GACAATGGTC
ACCGTCTCAA GC
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H47 (SEQ ID NO:197)
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        CA GGTGCAGCTA CAGCAGTGGG GCCCAGGACT GGTGAAGCCT TCGGGGACCC TGTCCCTCAC
CTGCGCTGTC TCTGGTGGCT CCATCAGCAG TAGTAACTGG TGGAGTTGGG TCCGCCAGCC CCCAGGGAAG
GGGCTGGAGT GGATTGGGGA AATCTATCAT AGTGGGAGCA CCAACTACAA CCCGTCCCTC AAGAGTCGAG
TCACCATATC AGTAGACAAG TCCAAGAACC AGTTCTCCCT GAAGCTGAGC TCTGTGACCG CCGCGGACAC
GGCCGTGTAT TACTGTGCGA GAGACAGCAG TGGCCAAGGG TACTTTGACT ACTGGGGCCA GGGCACCCTG
GTCACCGTCT CAAGC
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H48 (SEQ ID NO:199)
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GAGGTG CAGCTGGTGC AGTCTGGGGC TGAGGTGAAG AAGCCTGGGG CCTCAGTGAA GGTCTCCTGC
AAGGCTTCTG GATACACCTT CACTAGCTAT GCTATGCATT GGGTGCGCCA GGCCCCCGGA CAAAGGCTTG
AGTGGATGGG ATGGATCAAC GCTGGCAATG GTAACACAAA ATATTCACAG AAGTTCCAGG GCAGAGTCAC
CATGACCAGG GACACGTCCA CGAGCACAGT CTACATGGAG CTGAGCAGCC TGAGATCTGA GGACACGGCC
GTGTATTACT GTGCTAGACA CTCGTACTAC TACGGTATGG ACGTCTGGGG CCAAGGCACC CTGGTCACCG
TCTCAAGC
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H49 (SEQ ID NO:201)
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       CAG GTGCAGCTAC AGCAGTGGGG CGCAGGACTG TTGAAGCCTT CGGAGACCCT GTCCCTCACC
TGCGCTGTCT ATGGTGGGTC CTTCAGTGGT TACTACTGGA GCTGGATCCG CCAGCCCCCA GGGAAGGGGC
TGGAGTGGAT TGGGGAAATC AATCATAGTG GAAGCACCAA CTACAACCCG TCCCTCAAGA GTCGAGTCAC
CATATCGGTA GACACGTCCA AGAACCAGTT CTCCCTGAAG CTGAGCTCTG TGACCGCCGC GGACACGGCT
GTGTATTACT GTGCGAGAGT CGGGTATAGC ACGGCGAAG AAGTCCTGGA CGTCTGGGGC AAAGGGACCA
CGGTCACCGT CTCAAGC
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H50 (SEQ ID NO:203)
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      CAGGT GCAGCTGCAG GAGTCGGGCC CAGGACTGGT GAAGCCTTCG GAGACCCTGT CCCTCACCTG
CACTGTCTCT GGTGGCTCCA TCGGCAATTA TGACTGGAGT TGGATCCGGC AGCCCCCAGG GAAGGGACTG
GAGTGGATTG GGACTATCTA CTCTAGTGGG AGTACGTACT ACAGTCCGTC CCTCAAGAGT CGACTCACCA
TATCAGTAGA CAAGTCCAAG AACCGGTTCT CCCTGAAGCT GAGCTCTGTG ACCGCCGCGG ACACGGCCGT
GTATTACTGT GCGAGAGCAC GAGGGTATAG CAGCCCCTTC GACCCCTGGG GCCAGGGCAC CCTGGTCACC
GTCTCAAGC
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H51 (SEQ ID NO:205)
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        CA GGTCCAGCTG GTACAGTCTG GGGCTGAGGT GAAGAAGCCT GGGTCCTCGG TGAAGGTCTC
CTGCAAGGCT TCTGGAGGCA CCTTCAGCAG CTATGCTATC AGCTGGGTGC GACAGGCCCC TGGACAAGGG
CTTGAGTGGA TGGGAATAAT CAACCCTAGT GGTGGTAGCA CAAGCTACGC ACAGAAGTTC CAGGGCAGAG
TCACCATTAC CAGGGACACA TCCGCGAGCA CAGCCTACAT GGAGCTGAGC AGCCTGAGAT CTGAAGACAC
GGCTGTGTAT TACTGTGCGA GAGATCGGTG GAGGTACGAT GCTTTTGATA TCTGGGGCCA AGGGACAATG
GTCACCGTCT CAAGC
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H52 (SEQ ID NO:207)

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        G AGGTGCAGCT GGTGGAGTCT GGCCCAGGAC TGGTGAAGCC TTCGGGGACC CTGTCCCTCA
CCTGCGCTGT CTCTGGTGGC TCCATCAGCA GTAGTAACTG GTGGAGTTGG GTCCGCCAGC CCCCAGGGAA
GGGGCTGGAG TGGATTGGGG AAATCTATCA TAGTGGGAGC ACCAACTACA ACCCGTCCCT CAAGAGTCGA
GTCACCATAT CAGTAGACAA GTCCAAGAAC CAGTTCTCCC TGAAGCTGAG CTCTGTGACC GCCGCGGACA
CGGCCGTGTA TTACTGTGCG AGAGAAAAAT CGGGTATGGA CGTCTGGGGC CAAGGGACCA CGGTCACCGT
CTCAAGC
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Figure 2

LIGHT CHAIN VARIABLE REGION SEQUENCES

	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4	SEQ ID NO
L1	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSSGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPITF	GQGTRLEIK	2
L2	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPITF	GGGTRLEIK	4
L3	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	6
L4	EIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	8
L5	EIVLTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GPGTKVDIK	10
L6	DVVMTQSPLSLAVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	12
L7	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	14
L8	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	16
L9	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPITF	GQGTRLEIK	18
L10	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPFTF	GQGTRLEIK	20
L11	EIVLTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSASGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLAF	GQGTRLEIK	22
L12	NFMLTQPHSVSESPGKTVTISC	TRSSGSIASNYVQ	WYQQRPGSSPTTVIY	EDNQRPS	GVPDRFSGSIDSSSNSASLTISGLKTEDEADYYC	QSYDSSNQRVF	GGGTKLTVL	24
L13	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNTLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	26
L14	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	28
L15	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSYRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPITF	GQGTRLEIK	30
L16	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQGTHWPLTF	GQGTKVEIK	32
L17	EIVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	34
L18	DIQLTQSPSSVSASVGDRVTITC	RASQGISRWLA	WYQQKPGKAPRLLIY	AASGLQS	GVPSRFSGSGSGTDFTLTISNLQPEDFATYYC	QQASSFPITF	GQGTRLETK	36
L19	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPYTF	GQGTKLEIK	38
L20	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPNRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPFTF	GPGTKVDIK	40
L21	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSHGYNYLD	WYLQKPGQSPQLLIY	LGSYRAS	GVPDRFSGSHSGNTASLTITGAQAEDEADYYC	NSRDITGVHRF	GGGTKLEIK	42
L22	SSELTQDPAVSVALGQTVRITC	QGDSLRIYYTGN	WYQQKPGQAPVLVLF	GKNNRPS	GIPDRFSGSHSGNTASLTITGAQAEDEADYYC	NSRDITGVHRF	GGGTKLTVL	44
L23	EIVLTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	46
L24	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPNTF	GGGTKVEIK	48
L25	DVVMTQSPLSISASVGDRVTITC	RSSQGIGYFLN	WYQQEPGKAPKILISAA	STLQS	GVPSRFSGSGSGTDFTLSINNLQPADFATYYC	QQSHSPPYTF	GQGTKVEIK	50
L26	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYTYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEPEDVGVYYC	MQALEMPLTF	GGGTKVEIK	52
L27	DIQLTQSPSFLSASVGDRVTITC	RASQGISSYLA	WYQQKPGKAPKLLIY	AASTLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	QQLNSYPLTF	GGGTKVEIK	54
L28	SYVLTQPPSVSVSPGQTASITC	SGDKLGDKYVG	WYQQKAGQAPVLVIY	QDNKRPS	GIPERFSGSNSGNTASLTISGTQAMDEADYYC	QAWDSGTVF	GGGTKLTVL	56
L29	EIVLTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	58
L30	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPFTF	GPGTKVEIK	60
L31	DIQLTQSPSSLSASVGDRVTITC	RSSQGIGYFLNW	YQQEPGKAPKILISAA	STLQS	GVPSRFSGSGSGTDFTLSINNLQPADFATYYC	QQSHSPPYTF	GQGTKVEIK	62
L32	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	64
L33	EIVLTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIMY	IVSNRAS	GVPERFSGSGSGTDFTLKISRVEAEDVGVYYC	MQTLQTPLSF	GGGTRLEIK	66
L34	DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHSNGYNYLD	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC	MQALQTPLTF	GGGTKVEIK	68
L35	NFMLTQPHSVSASPGKTVTISC	TRSSGDIDNNYVQ	WYQQRPGNSPTNVIY	EDNRRPS	GVPDRFSGSIDSSSNSASLTISGLQPEDEADYYC	QSYQSIDNWVF	GGGTVTVL	70

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L36 NFMLTQPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSSPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSSNVFGGGTKLTVL
L37 DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPYTFGQGTRLEIK
L38 DVVMTQSPLSLPVTPGESASISCRSSQSLLHSNGYNFLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTKVEIK
L39 DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLTISSLEPEDFAVYYCQQRNNWPLTFGGGTKVEIK
L40 ETTLTQSPATLSLSPGQRATLSCRASQSVYNYLAWYQQKPGQAPRLLIYDASRRATGIPARFSGSGSGTDFTLTISSLQPEDFATYYCQQSNSVPLTFGGGTKVEIK
L41 DIQLTQSPSSLSASVGDSVTISCRASQSPGIFLNWYQQIPGKAPKLLIYAATSTLESGVPPRFTGSGSGTDFTLTISSLQPEDFATYYCQQSNSVPLTFGGGTKVEIK
L42 DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTRLEIK
L43 EIVMTQSPATLSVSPGERATFSCRASQSVGSNLAWYQQKPGQAPRLLIYDASNRAIGIPARFSGSGSGTDFTLTISRLEPEDFAVYYCQQRSNWPLTFGGGTKVEIK
L44 DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTKVEIK
L45 DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSTRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPYTFGGGTKVEIK
L46 DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGGTKVEIK
L47 DVVMTQSPLSLPVTPGEPASISCRSSQSLLHTNGYNYLDWYLQKPGQSPRLLIYLGFNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLQTPLTFGGGTKVEIK
L48 DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQATHWPYTFGQGTKLEIK
L49 NFMLTQPHSVSESPGKTVTISCTRNSGSIASNFVQWYQQRPGSAPTIVIYEDNQRPSGVPDRFSGSIDRSSNSASLTISGLTTEDEADYYCQSIDSANVIFGGGTKLTVL
L50 ETTLTQSPGTLSLSPGERATLSCRASQTISSSHLAWYQQKPGQSPRLLIYGAGYRATGLPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQHYGSSLRTFGQGTKVEIK
L51 NFMLTQPHSVSESPGKTVTISCTGSGGNIASNYVQWYQQRPGRAPTTVIYEDNRRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQSIDPYNRVFGGGTKLTVL
L52 EIVMTQSPLSLPVTPGEPASISCRSSQSLLHTNGYDYLDWYLQKPGQSPQLLIYLGSTRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQAFQTPLTFGGGTKMEIK

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Figure 3

HEAVY CHAIN VARIABLE REGION SEQUENCES

	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4	SEQ ID NO:
H1	EVQLVETGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	FNYIDSSV	WGQGTLVTVSS	106
H2	EVQLVETGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	GVEQIDW	GQGTLVTVSS	108
H3	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	NLAAGAVAYW	GQGTLVTVSS	110
H4	QVQLQQWGAGLLKPSETLSLTCAVSGGSF	GYIYWS	WIRQPPGKGLEWIGEINWSGST	NYNRSLKSR	VTISVDTSKNQFSLKLSSVTAADTAVYYCAR	LSYGSGVDYW	GQGTLVTVSS	112
H5	QLQLQESGPGLVKPSQTLSLTCTVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	YSSSRNDAFDIW	GQGTMVTVSS	114
H6	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	DGQLDAFDIW	GQGTMVTVSS	116
H7	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	FDYYGMDV	WGQGTTVTVSS	118
H8	QVQLQQWGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLESR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	DRIYGMDV	WGQGTTVTVSS	120
H9	EVQLVESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGYIYYSGGST	YNPSLKSR	VTMSVDTSKNQFSLKLSSVTAADTAVYYCAR	WSYLDAFDIW	GQGTMVTVSS	122
H10	EVQLVESGPGLVKPSETLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	DYDIFGMDV	WGQGTTVTVSS	124
H11	QLQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQSSLKLSSVTAADTAVYYCAR	ANRDDAFDIW	GQGTMVTVSS	126
H12	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	SYAMS	WVRQAPGKGLEWVSAISGSGGSTYYADSVKGR	FTISRDNSKNTLYLQMNSLSADDTAVFCASG	GWYGDYFGMDV	WGQGTLVTVSS	128
H13	QVQLVESGPGLVKPSETLSLTCTVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	EGNRTVTSAFDIW	GQGTMVTVSS	130
H14	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	GLGDSSGYILW	GQGTMVTVSS	132
H15	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	GLGDSSGYILW	GQGTMVTVSS	134
H16	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	WTGRTDAFDIW	GQGTMVTVSS	136
H17	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	QGALDAFDIW	GQGTLVTVSS	138
H18	EVQLVESGGGVVRPGGSLRLSCAASGFTFS	SYAMS	WVRQAPGKGLEWVSTISGSGGSTYYADSVKGR	FTISRDNSKNTLYLQMNSLRAEDTAVYYCAK	ERGSGWSLDNMDV	WGQGTTVTVSS	140
H19	QVQLVESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	DSSGFYGMDV	WGQGTMVTVSS	142
H20	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	SSWYWNAFDIW	GQGTMVTVSS	144
H21	QVQLQQWGPALVKPSGTLSLTCSVSVGSIT	SNIWWS	WIRQPPGKGPEWIGEVNPRGSTNVNPSLKSR	VTISVDTSKNQFSLKLSSVTAADTAVYYCAG	YRSFGESYW	GQGTLVTVSS	146
H22	QVQLQQWGAGLLKPSETLSLTCVVYGGSF	SDFYWS	WIRQPPGKGPEWIGEVNPGS	TNVNPSLKSR	ATISLDTSKNQFSLKLSSVTAADTAVYFCAR	GPRPGRDGYNYFDNW	GQGTLVTVSS	148
H23	QVQLQESGPGLVKPSGTLSLTCTVSGGSIS	SSYYWG	WIRQPPGKGLEWIGSIYYSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	GLAAAGQGDYW	GQGTLVTVSS	150
H24	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	DGGYTYGMDVW	GQGTTVTVSS	152
H25	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCASG	GYDAFDIW	GQGTTVTVSS	154
H26	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	YSYGTVGIDYW	GQGTLVTVSS	156
H27	EVQLVQSGGGVVQPGTSLRLSCAASGFSFR	SHGMH	WVRQAPGKGLEWVAVISYDGSNKYYADSVKGR	FTISRDNSKNTLYLQMNSLRAEDTAVYYCAT	IGPGGFDYW	GQGTLVTVSS	158
H28	QVQLQESGPGLVKPSGTLSLTCTVSGGSIRN	VYYWS	WIRQPPGKGLEWIGYISDSGNT	NYNPSLKSR	VTISVDTSKNQFSLKLTSVTATDTAAYFCARH	RSSWAWIFDLW	GQGTLVTVSS	160
H29	QVQLQESGPGLVKPSETLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	VGSGWNYVDYW	GQGTLVTVSS	162
H30	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	VSGYYYYGMDVW	GQGTTVTVSS	164
H31	EVQLVQSGGGVVQPGRSLRLSCAASGFTFS	SYGMEH	WVRQAPGKGLEWVAVISYDGSNKYYADSVKGR	FTISRDNSKNTLYLQMNSLRAEDTAVYYCAK	AYSSGWIDYYGMDV	WGRGTLVTVSS	166
H32	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	ASVDAFDIW	GQGTMVTVSS	168
H33	QVQLQESGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTAADTAVYYCAR	GLGDSSGYILW	GQGTLVTVSS	170
H34	QVQLQQSGPGLVKPSGTLSLTCAVSGGSIS	SSNWWS	WVRQPPGKGLEWIGEIYHSGST	NYNPSLKSR	VTISVDKSKNQFSLKLSSVTPEDTAVYYCAR	DHGPFDYW	GQGTLVTVSS	172

H35 QVQLVQSGGGVVQPGRSLRLSCAASGFAFSSYGMHWVRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRFGSGHLPDYWGQGTLVTVSS 174
H36 QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEIMHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVGYSSGRDVDYWGQGTLVTVSS 176
H37 EVQLVESGPGLVKPSGTLSLTCAVSGGSISSSNWMSWIRQPPGKGLEWIGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARDSSSWYYGMDVWGQGTLVTVSS 178
H38 EVQLVESGPGLVKPSETLSLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARSTWSLDYWGQGTLVTVSS 180
H39 EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRIIPILGIANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCAYLSFADPFDIWGQGTMVTVSS 182
H40 QVQLVQSGGGLVQPGGSLRLSCSASGFTFSSYAMHWVRQAPGKGLEYVSTISSNGDSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDKGIMDVWGKGTTVTVSS184
H41 EVQLVQSGGGLVQPGGSLRLSCSASGFTFSSYAMHWVRQAPGKGLEYVSTISSNGDSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKEEVWLQAFDIWGKGTTVSS 186
H42 QLQLQESGPGLVKPSETLSLTCTVSGGSISSSNWWSWVRQPPGKGLEWIGEIYHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAYMELSSLRSEDTAVYYCARDHRFDYAWLFDLWGRGTLVTVSS190
H43 QVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRIIPILGIANYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARDLTGSLDYWGQGTLVTVSS 192
H44 QVQLQESGPGLLKPSGTLSLTCAVSGGSISSSNWMSWVRQPPGEGLEWIGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARIRYDAFDIWGQGTMVTVSS 194
H45 QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCAVTAAHDAFDIWGQGTMVTVSS 196
H46 QVQLQQWGPGLVKPSGTLSLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARDSSGQGYFDYWGQGTLVTVSS 198
H47 EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYAMHWVRQAPGQRLEWMGWINAGNGNTKYSQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREHSYYYGMDVWGQGTLVTVSS 200
H48 QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEIMHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVGYSHGEEVLDVWGKGTTVTVSS 202
H49 QVQLQESGPGLVKPSETLSLTCTVSGGSIGNYDWSWIRQPPGKGLEWIGTIYSSGSTYYSPSLKSRLTISVDKSKNRFSLKLSSVTAADTAVYYCARARGYSSPFDPWGQGTLVTVSS 204
H50 QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCARDRWRYDAFDIWGQGTMVTVSS 206
H51 VQLVESGPGLVKPSGTLSLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGEIYHSGSTNYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCAREKSGMDVWGQGTTVTVSS 208

Figure 4

Light Chain   **CDR1 Sequence**

L2, L3, L4, L5,
L6, L7, L8, L9,
L10, L13, L14,
L15, L16, L17,
L19, L20, L23,
L24, L25, L29,
L30, L32, L33,
L34, L37, L39,
L42, L44, L45,

Light Chain	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
L46, L48	R	S	S	Q	S	L	L	H	S	N	G	Y	N	Y	L	D
L1	R	S	S	Q	S	L	L	H	S	S	G	Y	N	Y	L	D
L11	R	S	S	Q	S	L	L	H	S	N	G	Y	N	Y	L	N
L21	R	S	S	Q	S	L	L	H	S	H	G	Y	N	Y	L	D
L26	R	S	S	Q	S	L	L	H	S	N	G	Y	T	Y	L	D
L38	R	S	S	Q	S	L	L	H	S	N	G	Y	N	F	L	D
L47	R	S	S	Q	S	L	L	H	T	N	G	Y	N	Y	L	D
L52	R	S	S	Q	S	L	L	H	T	N	G	Y	D	Y	L	D
CONSENSUS	R	S	S	Q	S	L	L	H	S	N	G	Y	N	Y	L	D

Light Chain	T															
L51	T	G	S	G	G	N	I	A	S	N	Y	V	Q			
L12, L36	T	R	S	S	G	S	I	A	S	N	Y	V	Q			
L35	T	R	S	S	G	D	I	D	N	N	Y	V	Q			
L49	T	R	N	S	G	S	I	A	S	N	F	V	Q	W	Y	Q

									H		
L50	R	A	S	Q	T	I	S	S	S^	L	A
L18	R	A	S	Q	G	I	S	R	W	L	A
L27	R	A	S	Q	G	I	S	S	Y	L	A
L40	R	A	S	Q	S	V	Y	N	Y	L	A
L43	R	A	S	Q	S	V	G	S	N	L	A
L31	R	S	S	Q	G	I	G	Y	F	L	N
L41	R	A	S	Q	S	P	G	I	F	L	N
CONSENSUS	R	A	S	Q	G	I	G	X	Y	L	A
					S	V	S		F		N

Light Chain											
L28	S	G	D	K	L	G	D	K	Y	V	G
L22	Q	G	D	S	L	R	I	Y	Y	T	G

OVERALL CONSENSUS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	R	S	S	Q	S	L	X	X	X	X	X	X	X	X	X	X
						I										

Figure 5

Light Chain	CDR2 Sequence						
L1, L2, L3, L4, L5, L6, L7, L8, L9, L10, L11, L13, L14, L16, L17, L19, L20, L23, L24, L25, L26, L29, L30, L32, L34, L38, L39, L42, L44, L46, L48	L	G	S	N	R	A	S
L15, L21	L	G	S	Y	R	A	S
L33	L	V	S	N	R	A	S
L37	L	G	S	N	R	D	S
L45, L52	L	G	S	T	R	A	S
L47	L	G	F	N	R	A	S
CONSENSUS	L	G	S	N	R	A	S
L27, L31	A	A	S	T	L	Q	S
L18	A	A	S	G	L	Q	S
L41	A	T	S	T	L	E	S
CONSENSUS	A	A	S	T	L	Q	S
L12, L36, L49	E	D	N	Q	R	P	S
L35, L51	E	D	N	R	R	P	S
L28	Q	D	N	K	R	P	S
L22	G	K	N	N	R	P	S
CONSENSUS	E	D	N	X	R	P	S
L40	D	A	S	R	R	A	T
L43	D	A	S	N	R	A	T
L50	G	A	G	Y	R	A	T

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Figure 6

Light Chain	CDR3 Sequence								
L3, L5, L6, L7, L8 L13, L14, L17, L23, L29, L32, L34, L38, L39, L42, L44, L46	M	Q	A	L	Q	T	P	L	T
L52	M	Q	A	F	Q	T	P	L	T
L1, L2, L11, L15, L25	M	Q	A	L	Q	T	P	I	T
L19, L45	M	Q	A	L	Q	T	P	Y	T
L9, L20	M	Q	A	L	Q	T	P	F	T
L4	M	Q	A	L	Q	T	P	H	T
L24	M	Q	A	L	Q	T	P	N	T
L10	M	Q	A	L	Q	T	P	L	A
L47	M	Q	G	L	Q	T	P	L	T
L26	M	Q	A	L	E	M	P	L	T
L30	M	E	A	L	Q	T	P	F	T
L33	M	Q	T	L	Q	T	P	L	S
L16	M	Q	G	T	H	W	P	L	T
L21	M	Q	S	L	E	V	P	F	T
L48	M	Q	A	T	H	W	P	Y	T
L37	M	Q	G	T	H	W	P	Y	T
CONSENSUS	M	Q	A	L	Q	T	P	*	T

"*" = *nonpolar side chain amino acid*

	CDR3 Sequence								
L40	Q	Q	R	N	N	W	P	L	T
L43	Q	Q	R	S	N	W	P	L	T
L41	Q	Q	S	N	S	V	P	L	T
L27	Q	Q	L	N	S	Y	P	L	T
L31	Q	Q	S	H	S	P	P	Y	T
L18	Q	Q	A	S	S	F	P	I	T
CONSENSUS	Q	Q	R	N	S	*	P	L	T
			S	S	N				
				S	N				

"*" = *nonpolar side chain amino acid*

	CDR3 Sequence								
L12	Q	S	Y	D	S	S	N	Q	R	V
L51	Q	S	Y	D	P	Y	N	R	V
L36	Q	S	Y	D	S	S	N	V	–	V
L35	Q	S	Y	Q	S	D	N	W	–	V
L49	Q	S	Y	D	S	A	N	V	I
	Q	S	Y	D	S	S	N	X	V

	CDR3 Sequence							
L28	Q	A	W	D	S	G	T	V

	CDR3 Sequence							
L50	Q	H	Y	G	S	S	L	R	T

	CDR3 Sequence							
L22	N	S	R	D	I	T	G	V	H	R

Figure 7

Heavy Chain	CDR1 Sequence					
H1, H2, H3, H5, H6, H7, H8, H9, H10, H11, H13, H14, H15, H16, H17, H19, H20, H23, H25, H26, H29, H30, H32, H33, H34, H37,						
H38, H39, H44, H46, H47, H52	S	S	N	W	W	S
H42, H45	–	S	N	W	W	S
H21	S	N	I	W	W	S
CONSENSUS	S	S	N	W	W	S
H4, H36, H49	G	Y	Y	W	S	
H50	N	Y	D	W	S	
H28	N	Y	Y	W	S	
H22	D	F	Y	W	S	
CONSENSUS	X	Y	Y	W	S	
H12, H18	S	Y	A	M	S	
H40, H43, H51	S	Y	A	I	S	
H31, H35	S	Y	G	M	H	
H41, H48	S	Y	A	M	H	
CONSENSUS	S	Y	A	M	S H	
H27	S	H	G	M	H	
H24	S	S	S	Y	Y	W	G

Figure 8

Heavy Chain						CDR2 Sequence										
H1, H2, H3, H5, H6, H7, H10, H11, H13, H14, H15, H16, H17, H19, H20, H23, H25, H26, H29, H30, H32, H33, H34, H37, H38, H39, H42, H44, H45, H46, H47, H52	E	I	Y	H	S	G	S	T	N	Y	N	P	S	L	K	S
H8	E	I	Y	H	S	G	S	T	N	Y	N	P	S	L	E	S
H36, H49	E	I	N	H	S	G	S	T	N	Y	N	P	S	L	K	S
H21	E	V	Y	H	S	G	S	T	N	Y	N	P	S	L	K	S
H4	E	I	N	H	S	G	S	T	N	Y	N	R	S	L	K	S
H9	Y	I	Y	Y	S	G	S	T	Y	Y	N	P	S	L	K	S
H50	T	I	Y	S	S	G	S	T	Y	Y	S	P	S	L	K	S
H24	S	I	Y	Y	S	G	S	T	Y	Y	N	P	S	L	K	S
H28	Y	I	S	D	S	G	N	T	N	Y	N	P	S	L	K	S
H22	E	V	N	P	R	G	S	T	N	Y	N	P	S	L	K	S
CONSENSUS	E	I	Y	H	S	G	S	T	N	Y	N	P	S	L	K	S
	Y	V	N	Y					Y							

Heavy Chain																	
H18	T	I	S	G	S	G	G	S	T	Y	Y	A	D	S	V	K	G
H12	A	I	S	G	S	G	G	S	T	Y	Y	A	D	S	V	K	G
H41	T	I	S	S	N	G	D	S	T	Y	Y	A	D	S	V	K	G
H27, H31	V	I	S	Y	D	G	S	N	K	Y	Y	A	D	S	V	K	G
H35	Y	I	S	S	S	S	S	T	I	Y	Y	A	D	S	V	K	G
CONSENSUS	X	I	S	G	S	G	G	S	T	Y	Y	A	D	S	V	K	G
				S			S										

Heavy Chain																	
H40, H43	R	I	I	P	I	L	G	I	A	N	Y	A	Q	K	F	Q	G
H48	W	I	N	A	G	N	G	N	T	K	Y	S	Q	K	F	Q	G
H51	I	I	N	P	S	G	G	S	T	S	Y	A	Q	K	F	Q	G

Figure 9

Heavy Chain CDR3 Sequence

H5	–	Y	S	S	S	R	N	D	A	F	D	I
H6	–	–	–	D	G	Q	L	D	A	F	D	I
H9	–	–	–	W	S	Y	L	D	A	F	D	I
H11	–	–	–	A	N	R	D	D	A	F	D	I
H13	E	G	N	R	T	V	T	S	A	F	D	I
H16	–	–	W	T	G	R	T	D	A	F	D	I
H17	–	–	–	Q	G	A	L	D	A	F	D	I
H20	–	S	S	S	W	Y	W	N	A	F	D	I
H25	–	–	–	–	S	G	Y	D	A	F	D	I
H32	–	–	–	–	A	S	V	D	A	F	D	I
H39	–	–	–	L	S	F	A	D	P	F	D	I
H41	–	–	E	E	V	W	L	Q	A	F	D	I
H45	–	–	–	–	I	R	Y	D	A	F	D	I
H46	–	–	–	T	A	A	H	D	A	F	D	I
H51			D	R	W	R	Y	D	A	F	D	I
CONSENSUS	–	–	–	X	S	R	L	D	A	F	D	I

H7		–	–	–	–	–	F	W	D	Y	Y	G	M	D	V
H52									E	K	S	G	M	D	V
H8		–	–	–	–	–	–	D	R	Y	Y	G	M	D	V
H10		–	–	–	–	–	D	Y	D	I	F	G	M	D	V
H18		–	E	R	G	S	G	W	S	L	D	N	M	D	V
H19		–	–	–	–	D	S	S	G	F	Y	G	M	D	V
H24		–	–	–	D	G	G	Y	Y	Y	Y	G	M	D	V
H48								H	S	Y	Y	Y	G	M	D	V
H30		–	–	–	V	S	G	Y	Y	Y	Y	G	M	D	V
H31		A	Y	S	S	G	W	Y	D	Y	Y	G	M	D	V
H37		–	–	–	D	S	S	S	W	Y	Y	G	M	D	V
H40		–	G	S	G	S	Y	Y	D	Y	Y	Y	M	D	V
H42		–	–	–	–	–	–	–	D	K	G	Y	M	D	V
CONSENSUS		–	–	–	–	S	X	Y	D	Y	Y	G	M	D	V

H2	–	–	–	–	G	V	E	Q	I	D	Y
H3	–	–	N	L	A	A	G	A	V	A	Y
H4	–	–	L	S	Y	G	S	G	V	D	Y
H12	–	G	G	W	Y	G	D	Y	F	D	Y
H23	–	G	I	A	A	A	G	Q	G	D	Y
H26	–	Y	S	Y	G	T	V	G	I	D	Y
H27	–	–	–	I	G	P	G	G	F	D	Y
H29	–	–	V	G	S	G	W	Y	V	D	Y
H34	–	–	–	–	D	H	G	P	F	D	Y
H35	D	R	F	G	S	G	H	L	P	D	Y
H36	V	G	Y	S	S	G	R	D	V	D	Y
H38	–	–	–	–	S	T	W	S	L	D	Y
H44	–	–	–	D	L	T	G	S	L	D	Y
H47	–	D	S	S	G	Q	G	Y	F	D	Y
CONSENSUS	–	–	X	X	G	G	G	X	*	D	Y

"*" = nonpolar side chain amino acids

H22	G	P	R	P	G	R	D	G	Y	N	Y	F	D	N
H28	–	–	–	H	R	S	S	W	A	W	Y	F	D	L
H43	–	–	D	H	R	F	D	Y	A	W	Y	F	D	L
CONSENSUS	–	–	X	H	R	X	D	X	A	W	Y	F	D	L

H1	F	N	Y	Y	D	S	S	V						
H14, H15, H33	–	G	L	G	D	S	S	G	Y	I	L			
H19	–	–	–	–	D	S	S	G	F	Y	G	M	D	V
H37	–	–	–	–	D	S	S	S	W	Y	Y	G	M	D	V

H47	–	–	–	–	D	S	S	G	Q	G	Y	F	D	Y
CONSENSUS	–	–	–	–	D	S	S	G	X	X	X	–	–	–

H21	Y	R	S	F	G	E	S	Y		

H49	V	G	Y	S	H	G	E	E	V	L	D	V

H50	A	R	G	Y	S	S	P	F	D	P

Figure 10

```
   1 MKSGSGGGSP TSLWGLLFLS AALSLWPTSG EICGPGIDIR NDYQQLKRLE NCTVIEGYLH

  61 ILLISKAEDY RSYRFPKLTV ITEYLLLFRV AGLESLGDLF PNLTVIRGWK LFYNYALVIF

 121 EMTNLKDIGL YNLRNITRGA IRIEKNADLC YLSTVDWSLI LDAVSNNYIV GNKPPKECGD

 181 LCPGTMEEKP MCEKTTINNE YNYRCWTTNR CQKMCPSTCG KRACTENNEC CHPECLGSCS

 241 APDNDTACVA CRHYYYAGVC VPACPPNTYR FEGWRCVDRD FCANILSAES SDSEGFVIHD

 301 GECMQECPSG FIRNGSQSMY CIPCEGPCPK VCEEKKTKT IDSVTSAQML QGCTIFKGNL

 361 LINIRRGNNI ASELENFMGL IEVVTGYVKI RHSHALVSLS FLKNLRLILG EEQLEGNYSF

 421 YVLDNQNLQQ LWDWDHRNLT IKAGKMYFAF NPKLCVSEIY RMEEVTGTKG RQSKGDINTR

 481 NNGERASCES DVLHFTSTTT SKNRIIITWH RYRPPDYRDL ISFTVYYKEA PFKNVTEYDG

 541 QDACGSNSWN MVDVDLPPNK DVEPGILLHG LKPWTQYAVY VKAVTLTMVE NDHIRGAKSE

 601 ILYIRTNASV PSIPLDVLSA SNSSSQLIVK WNPPSLPNGN LSYYIVRWQR QPQDGYLYRH

 661 NYCSKDKIPI RKYADGTIDI EEVTENPKTE VCGGEKGPCC ACPKTEAEKQ AEKEEAEYRK

 721 VFENFLHNSI FVPRPERKRR DVMQVANTTM SSRSRNTTAA DTYNITDPEE LETEYPFFES

 781 RVDNKERTVI SNLRPFTLYR IDIHSCNHEA EKLGCSASNF VFARTMPAEG ADDIPGPVTW

 841 EPRPENSIFL KWPEPENPNG LILMYEIKYG SQVEDQRECV SRQEYRKYGG AKLNRLNPGN

 901 YTARIQATSL SGNGSWTDPV FFYVQAKTGY ENFIHLDEVD GCKPCICTVP EVSSVFIFPP

 961 KPKDVLTITL TPKVTCVVVD ISKDDPEVQF SWFVDDVEVH TAQTQPREEQ FNSTFRSVSE

1021 LPIMHQDWLN GKEFKCRVNS AAFPAPIEKT ISKTKGRPKA PQVYTIPPPK EQMAKDKVSL

1081 TCMITDFFPE DITVEWQWNG QPAENYKNTQ PIMDTDGSYF VYSKLNVQKS NWEAGNTFTC

1141 SVLHEGLHNH HTEKSLSHSP GK
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Figure 11

```
   1 MGTGGRRGAA AAPLLVAVAA LLLGAAGHLY PGEVCPGMDI RNNLTRLHEL ENCSVIEGHL
  61 QILLMFKTRP EDFRDLSFPK LIMITDYLLL FRVYGLESLK DLFPNLTVIR GSRLFFNYAL
 121 VIFEMVHLKE LGLYNLMNIT RGSVRIEKNN ELCYLATIDW SRILDSVEDN HIVLNKDDNE
 181 ECGDICPGTA KGKTNCPATV INGQFVERCW THSHCQKVCP TICKSHGCTA EGLCCHSECL
 241 GNCSQPDDPT KCVACRNFYL DGRCVETCPP PYYHFQDWRC VNFSFCQDLH HKCKNSRRQG
 301 CHQYVIHNNK CIPECPSGYT MNSSNLLCTP CLGPCPKVCH LLEGEKTIDS VTSAQELRGC
 361 TVINGSLIIN IRGGNNLAAE LEANLGLIEE ISGYLKIRRS YALVSLSFFR KLRLIRGETL
 421 EIGNYSFYAL DNQNLRQLWD WSKHNLTTTQ GKLFFHYNPK LCLSEIHKME EVSGTKGRQE
 481 RNDIALKTNG DKASCENELL KFSYIRTSFD KILLRWEPYW PPDFRDLLGF MLFYKEAPYQ
 541 NVTEFDGQDA CGSNSWTVVD IDPPLRSNDP KSQNHPGWLM RGLKPWTQYA IFVKTLVTFS
 601 DERRTYGAKS DIIYVQTDAT NPSVPLDPIS VSNSSSQIIL KWKPPSDPNG NITHYLVFWE
 661 RQAEDSELFE LDYCLKGLKL PSRTWSPPFE SEDSQKHNQS EYEDSAGECC SCPKTDSQIL
 721 KELEESSFRK TFEDYLHNVV FVPRKTSSGT GAEDPRPSRK RRSLGDVGNV TVAVPTVAAF
 781 PNTSSTSVPT SPEEHRPFEK VVNKESLVIS GLRHFTGYRI ELQACNQDTP EERCSVAAYV
 841 SARTMPEAKA DDIVGPVTHE IFENNVVHLM WQEPKEPNGL IVLYEVSYRR YGDEELHLCV
 901 SRKHFALERG CRLRGLSPGN YSVRIRATSL AGNGSWTEPT YFYVTDYLDV PSNIAKVDGC
 961 KPCICTVPEV SSVFIFPPKP KDVLTITLTP KVTCVVVDIS KDDPEVQFSW FVDDVEVHTA
1021 QTQPREEQFN STFRSVSELP IMHQDWLNGK EFKCRVNSAA FPAPIEKTIS KTKGRPKAPQ
1081 VYTIPPPKEQ MAKDKVSLTC MITDFFPEDI TVEWQWNGQP AENYKNTQPI MDTDGSYFVY
1141 SKLNVQKSNW EAGNTFTCSV LHEGLHNHHT EKSLSHSPGK
```

Figure 12

```
   1     MKSGSGGG SPTSLWGLLF LSAALSLWPT SGEICGPGID IRNDYQQLKR

  51     LENCTVIEGY LHILLISKAE DYRSYRFPKL TVITEYLLLF RVAGLESLGD

 101     LFPNLTVIRG WKLFYNYALV IFEMTNLKDI GLYNLRNITR GAIRIEKNAD

 151     LCYLSTVDWS LILDAVSNNY IVGNKPPKEC GDLCPGTMEE KPMCEKTTIN

 201     NEYNYRCWTT NRCQKMCPST CGKRACTENN ECCHPECLGS CSAPDNDTAC

 251     VACRHYYYAG VCVPACPPNT YRFEGWRCVD RDFCANILSA ESSDSEGFVI

 301     HDGECMQECP SGFIRNGSQS MYCIPCEGPC PKVCEEKKT KTIDSVTSAQ

 351     MLQGCTIFKG NLLINIRRGN NIASELENFM GLIEVVTGYV KIRHSHALVS

 401     LSFLKNLRLI LGEEQLEGNY SFYVLDNQNL QQLWDWDHRN LTIKAGKMYF

 451     AFNPKLCVSE IYRMEEVTGT KGRQSKGDIN TRNNGERASC ESDVLHFTST

 501     TTSKNRIIIT WHRYRPPDYR DLISFTVYYK EAPFKNVTEY DGQDACGSNS

 551     WNMVDVDLPP NKDVEPGILL HGLKPWTQYA VYVKAVTLTM VENDHIRGAK

 601     SEILYIRTNA SVPSIPLDVL SASNSSSQLI VKWNPPSLPN GNLSYYIVRW

 651     QRQPQDGYLY RHNYCSKDKI PIRKYADGTI DIEEVTENPK TEVCGGEKGP

 701     CCACPKTEAE KQAEKEEAEY RKVFENFLHN SIFVPRPERK RRDVMQVANT

 751     TMSSRSRNTT AADTYNITDP EELETEYPFF ESRVDNKERT VISNLRPFTL

 801     YRIDIHSCNH EAEKLGCSAS NFVFARTMPA EGADDIPGPV TWEPRPENSI

 851     FLKWPEPENP NGLILMYEIK YGSQVEDQRE CVSRQEYRKY GGAKLNRLNP

 901     GNYTARIQAT SLSGNGSWTD PVFFYVQAKT GYEAAAARKC SLTGKWTNDL

 951     GSNMTIGAVN SKGEFTGTYT TAVTATSNEI KESPLHGTQN TINKRTQPTF

1001     GFTVNWKFSE STTVFTGQCF IDRNGKEVLK TMWLLRSSVN DIGDDWKATR

1101     VGINIFTRLR TQKE
```

Figure 13

Kappa light chain constant region

Nucleotide Sequence

cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgc
tgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagt
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acacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt

Amino acid sequence

rtvaapsvfifppsdeqlksgtasvvcllnnfypreakvqwkvdnalqsgnsqesvteqdskdstysls
stltlskadyekhkvyacevthqglsspvtksfnrgec

IgG1 heavy chain constant region

Nucleotide Sequence

gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctggggggcacagcggccctgggct
gcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttc
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Amino acid sequence

astkgpsvfplapsskstsggtaalgclvkdyfpepvtvswnsgaltsgvhtfpavlqssglyslssvv
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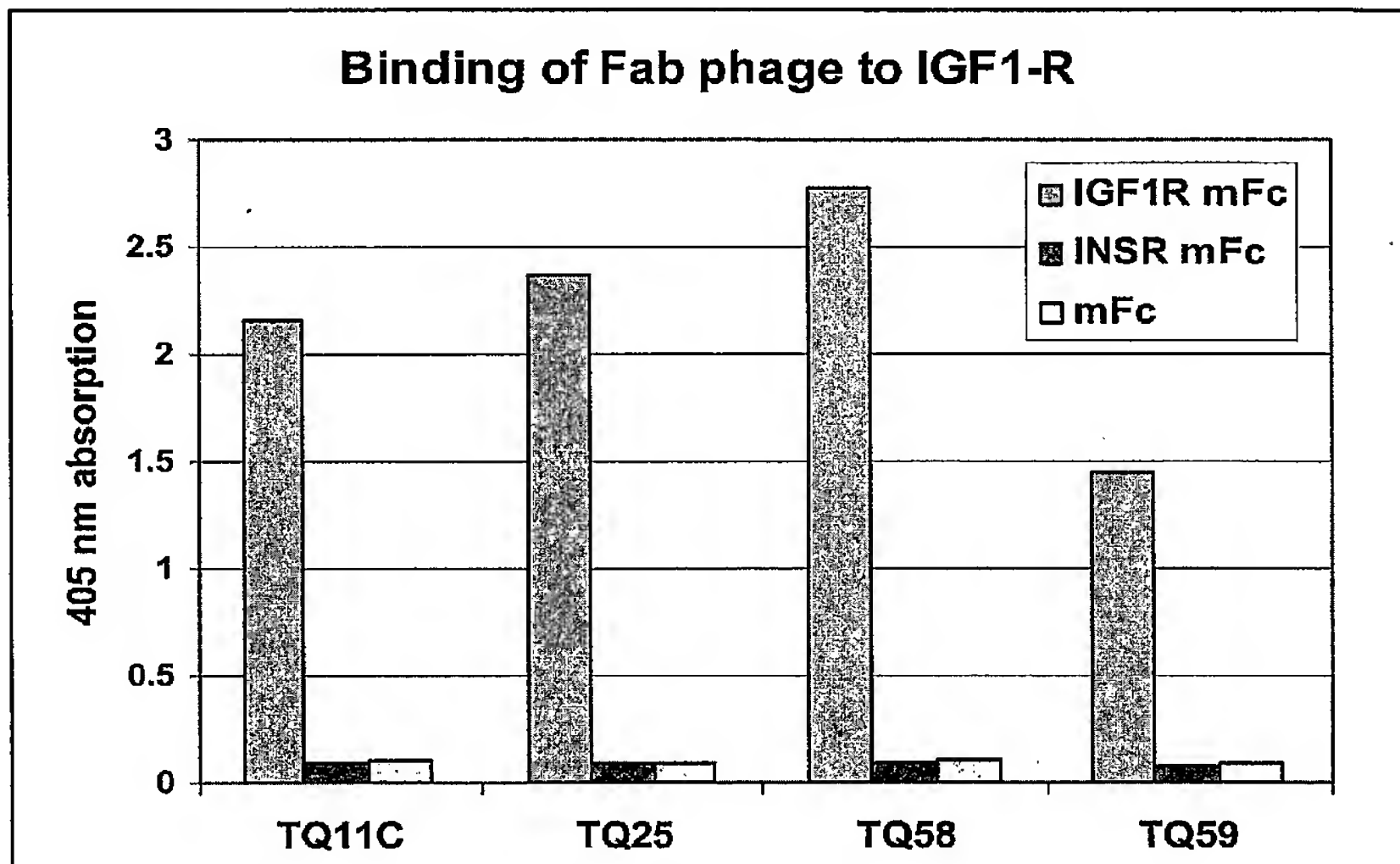
Figure 14

Figure 15
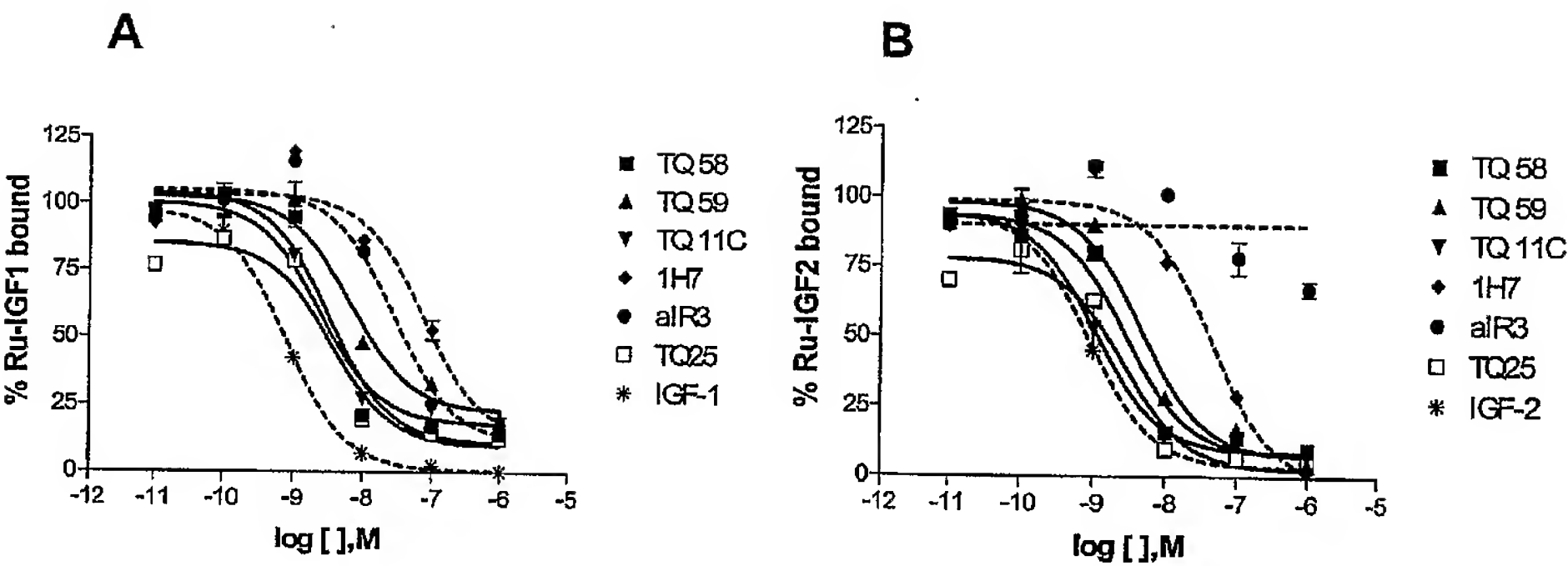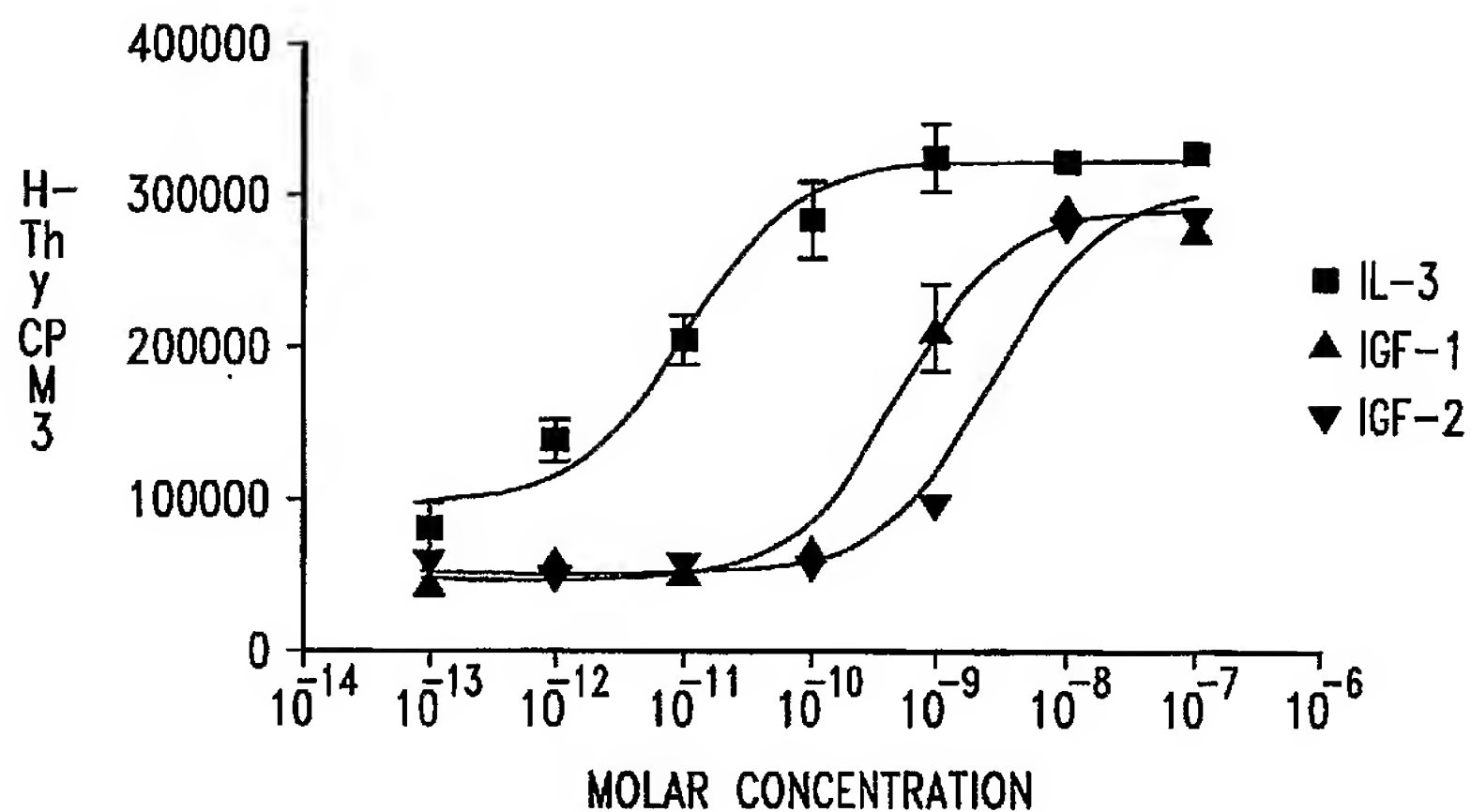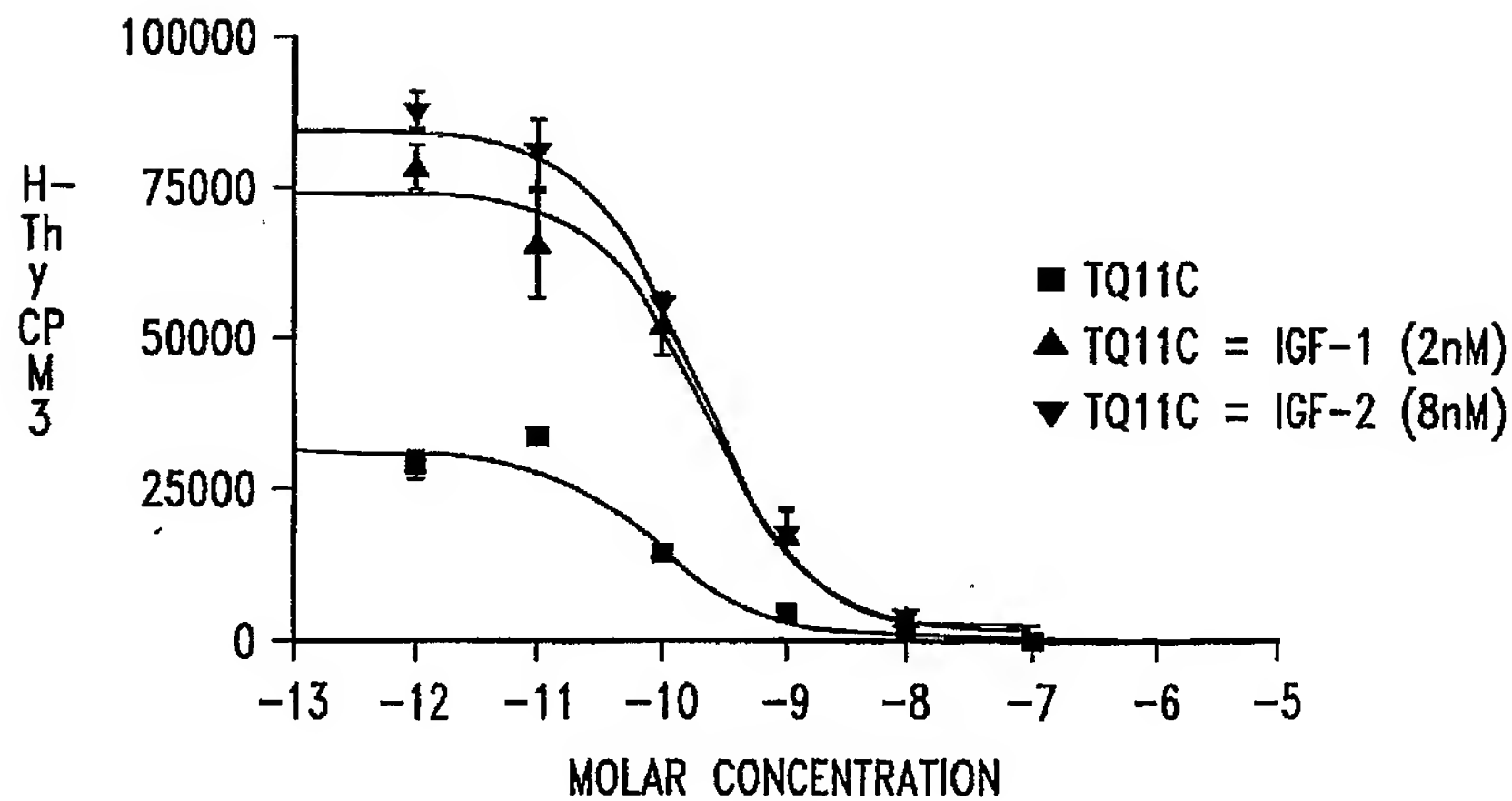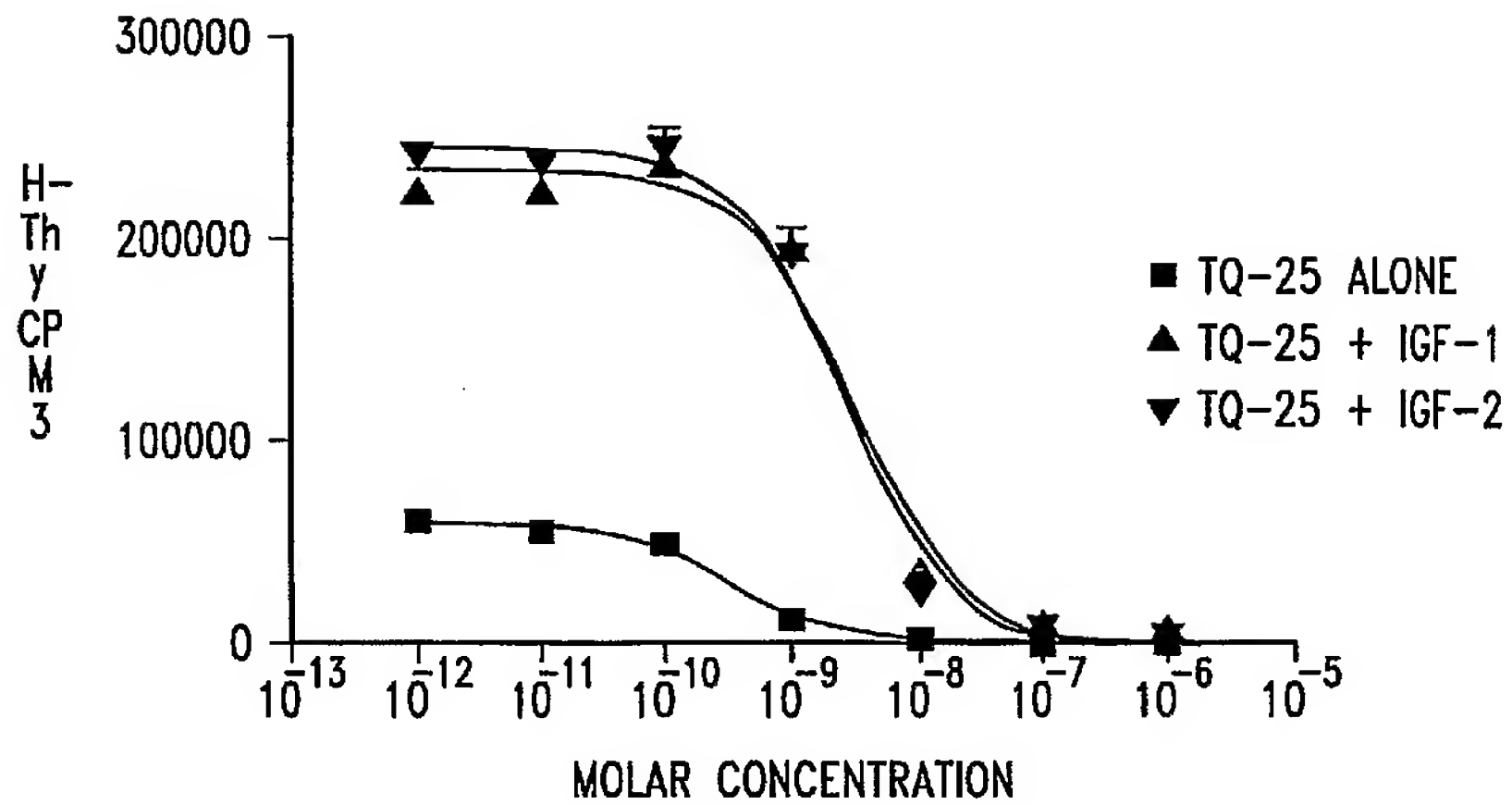
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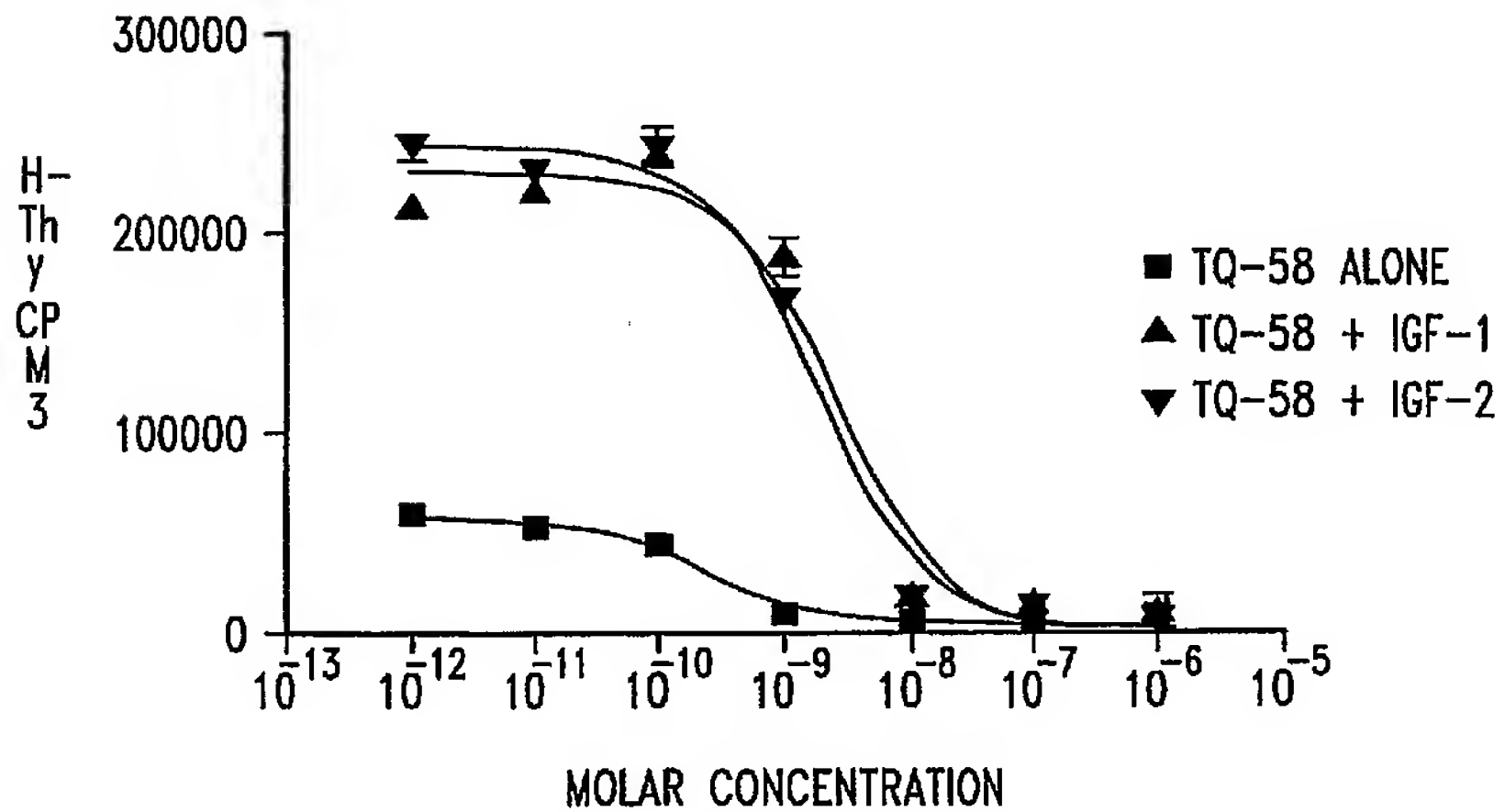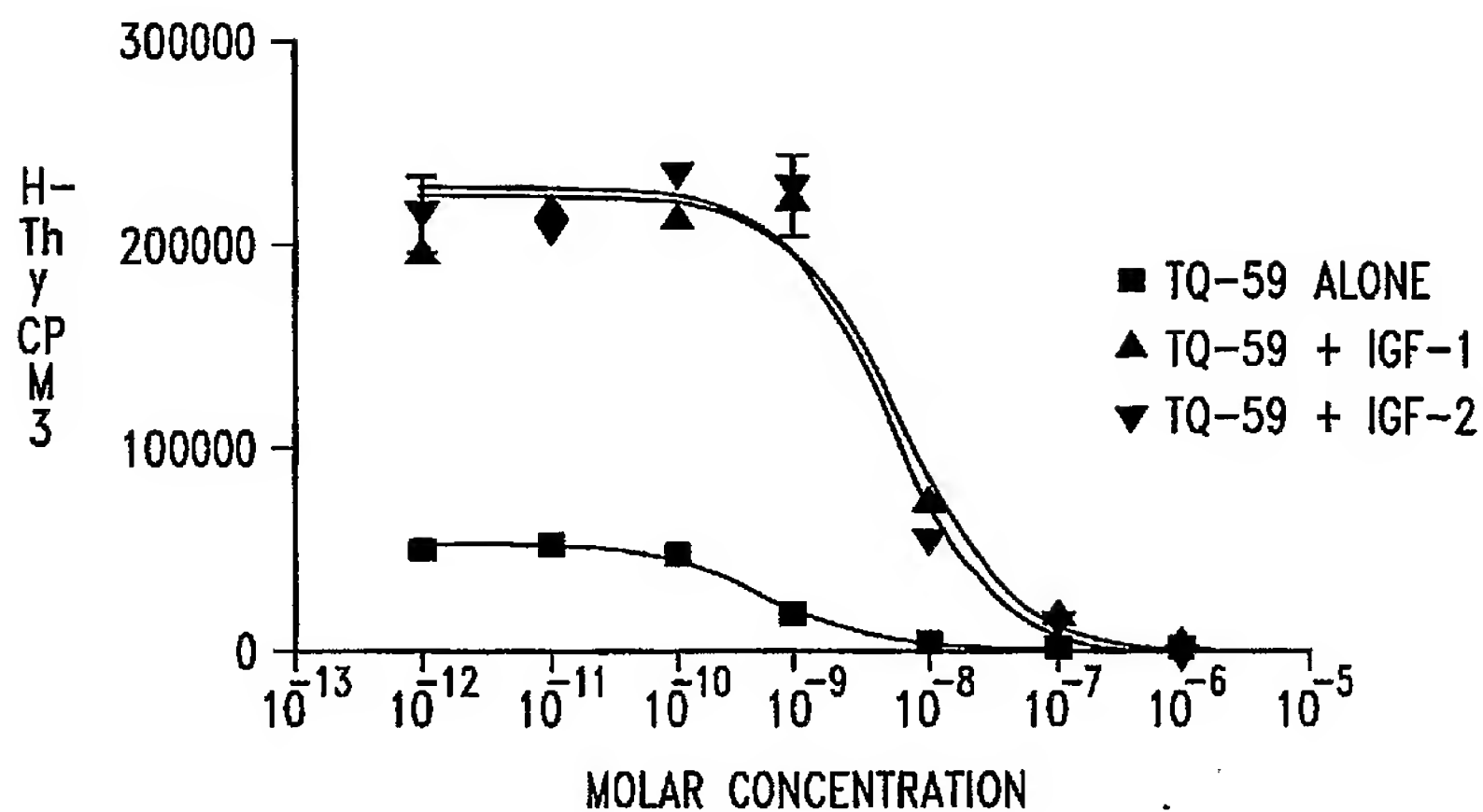
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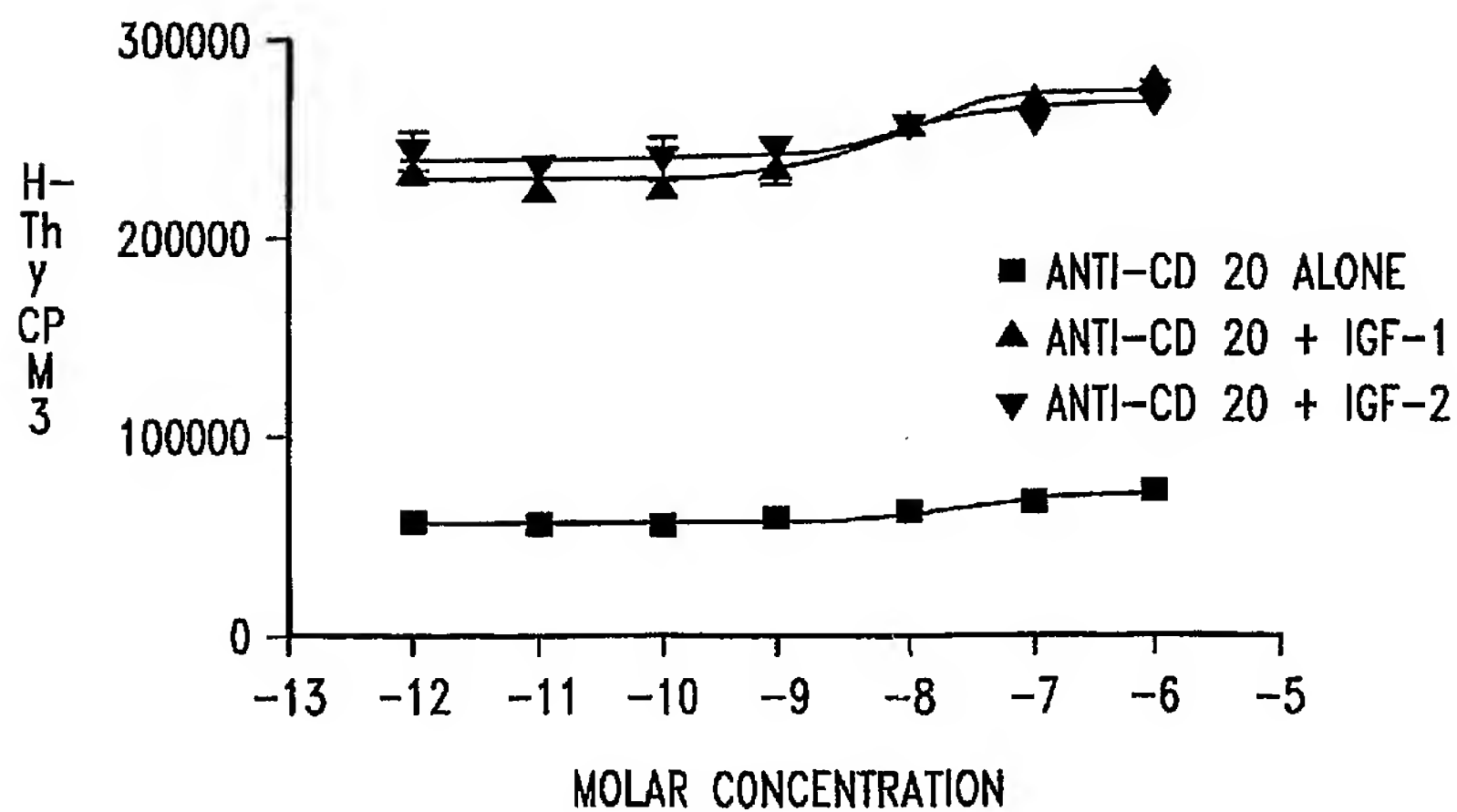
Fig. 16B

Fig. 16C

Fig. 16D

Fig. 16E

Fig. 16F
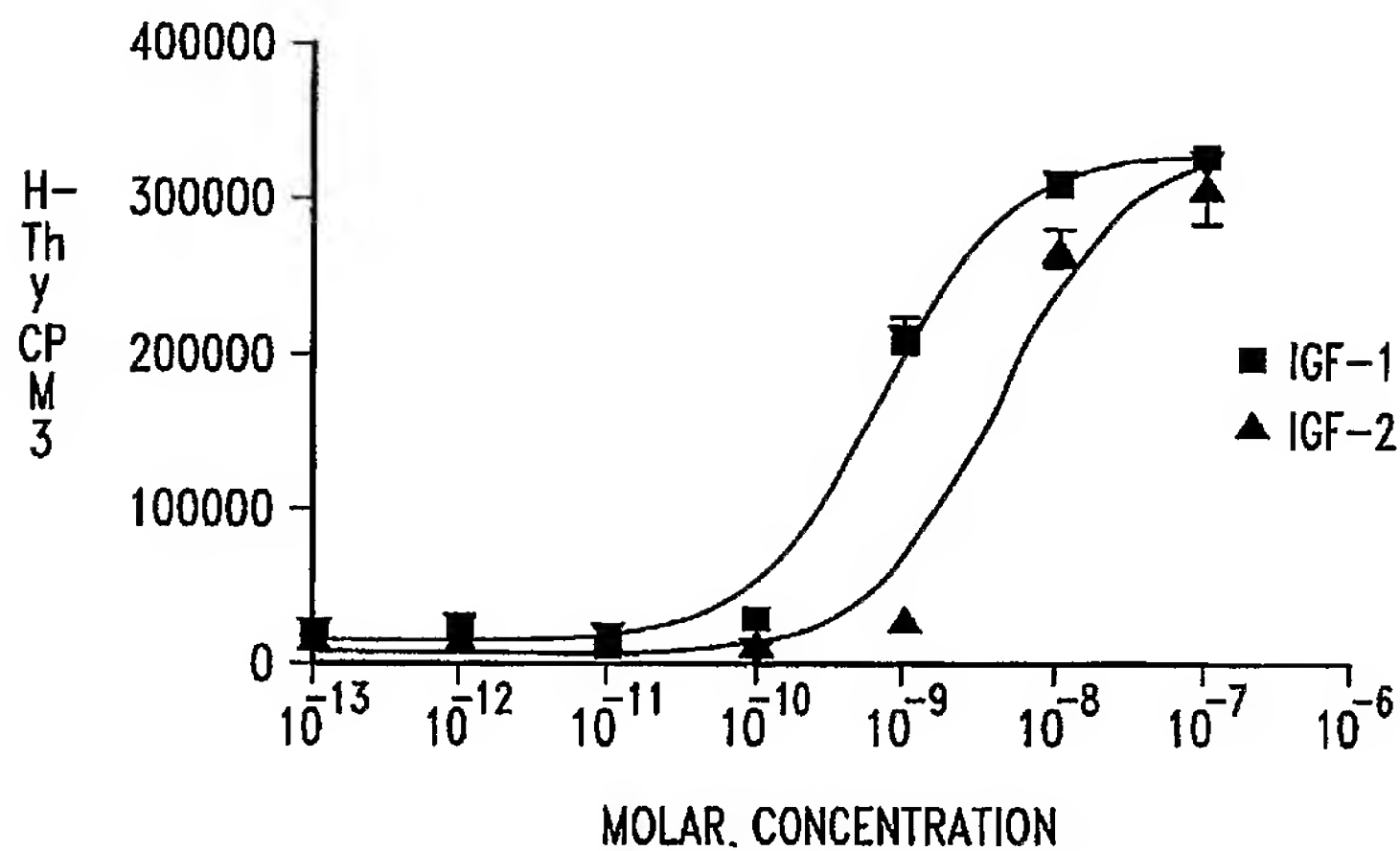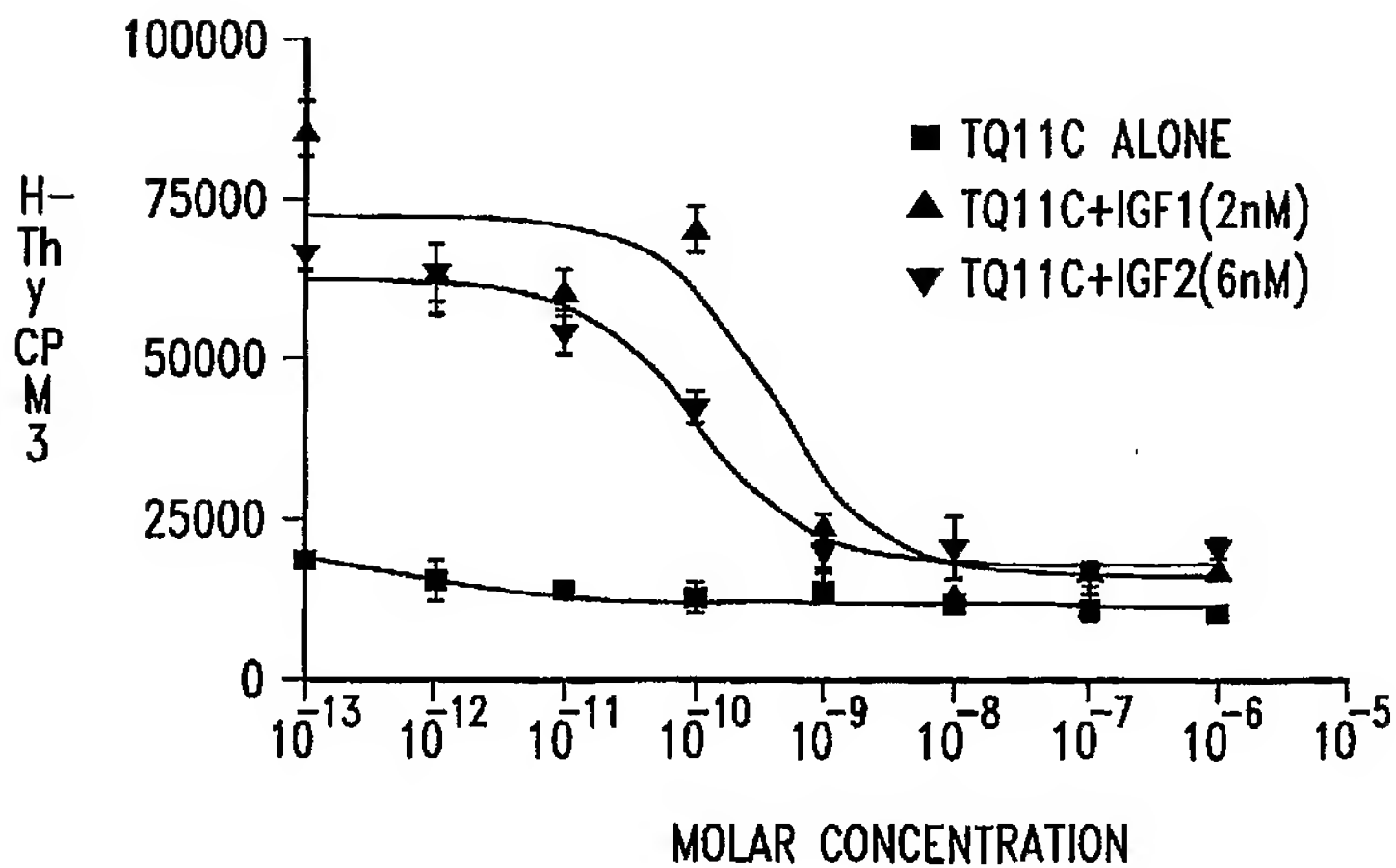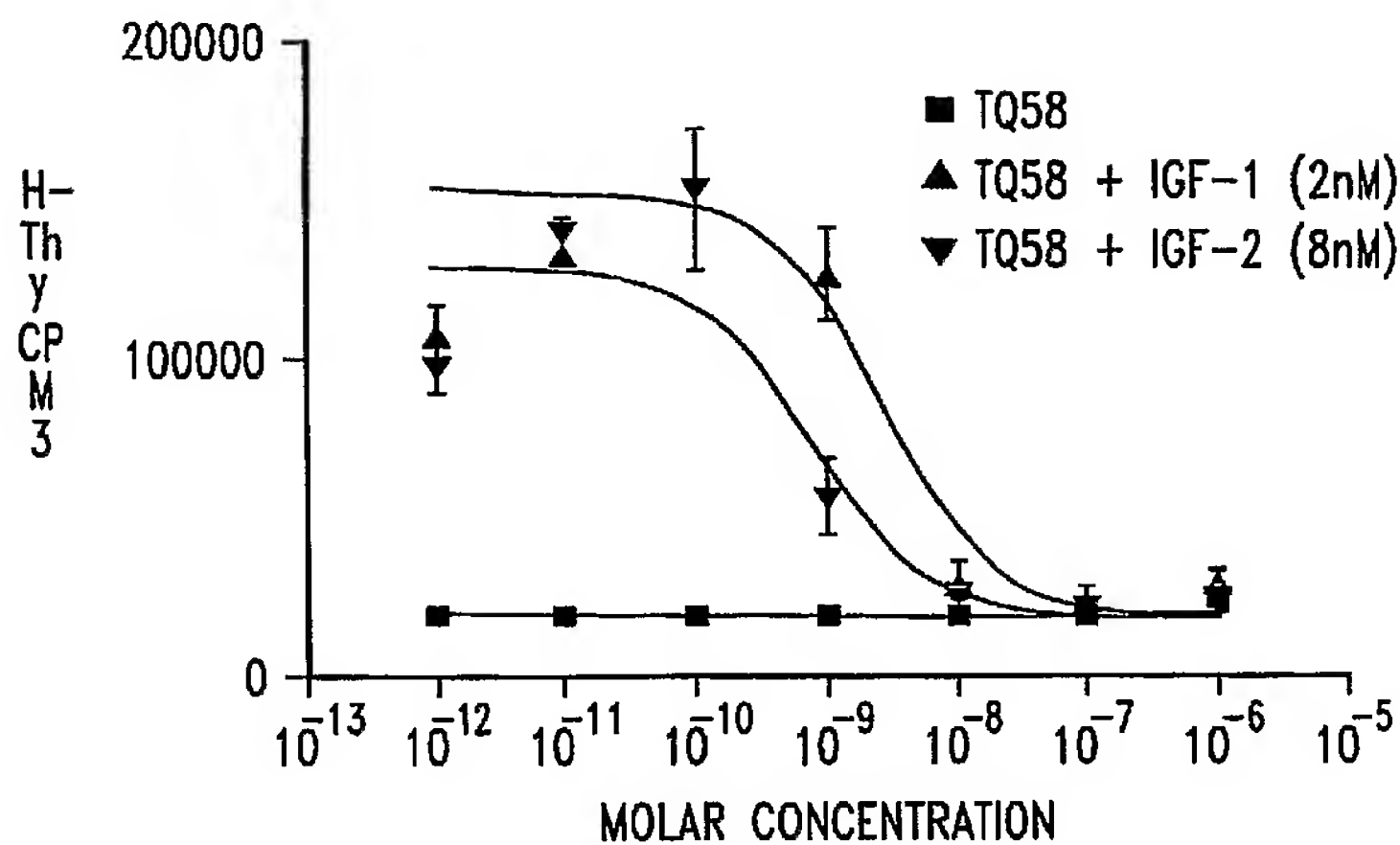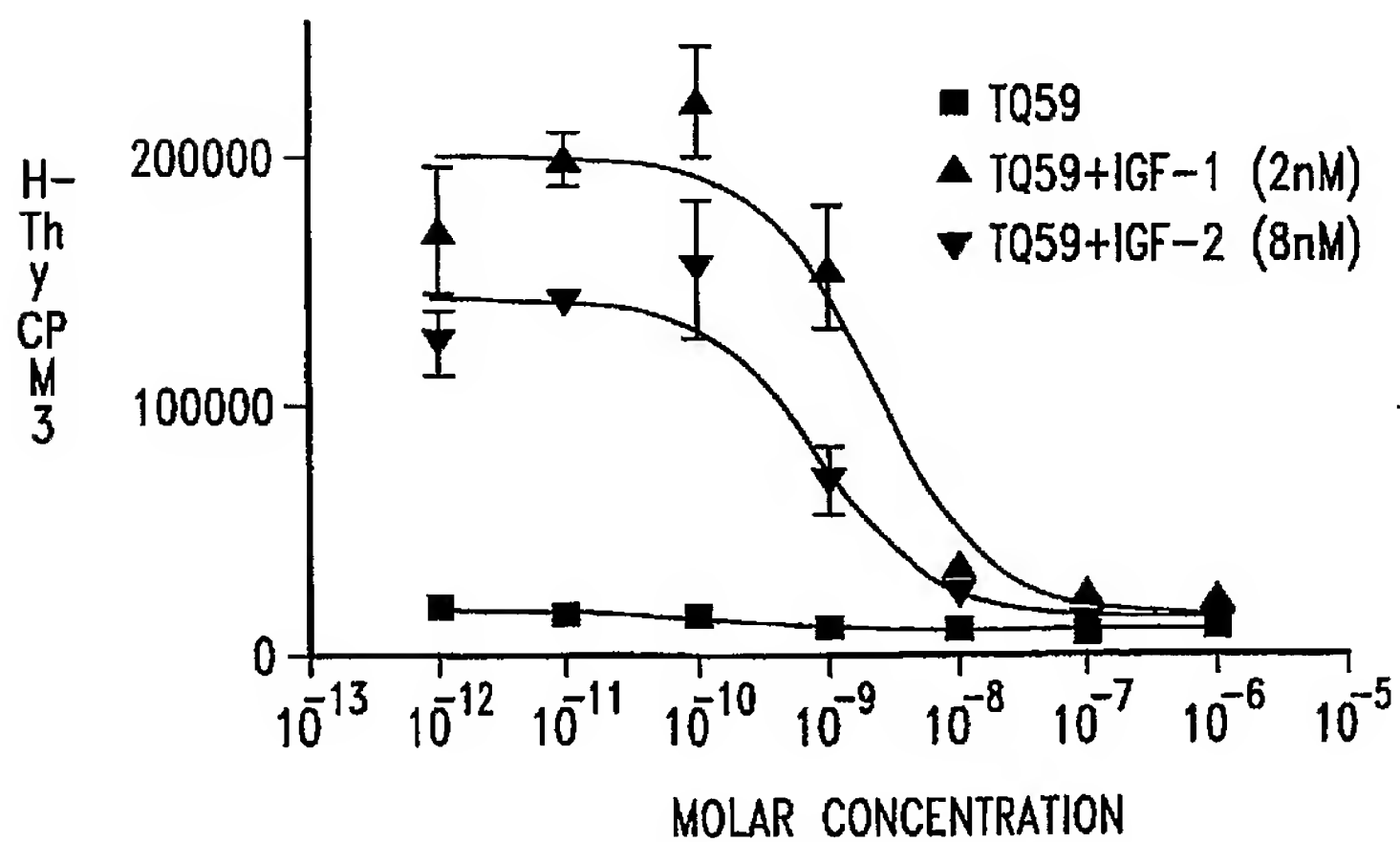
Fig. 17A

Fig. 17B
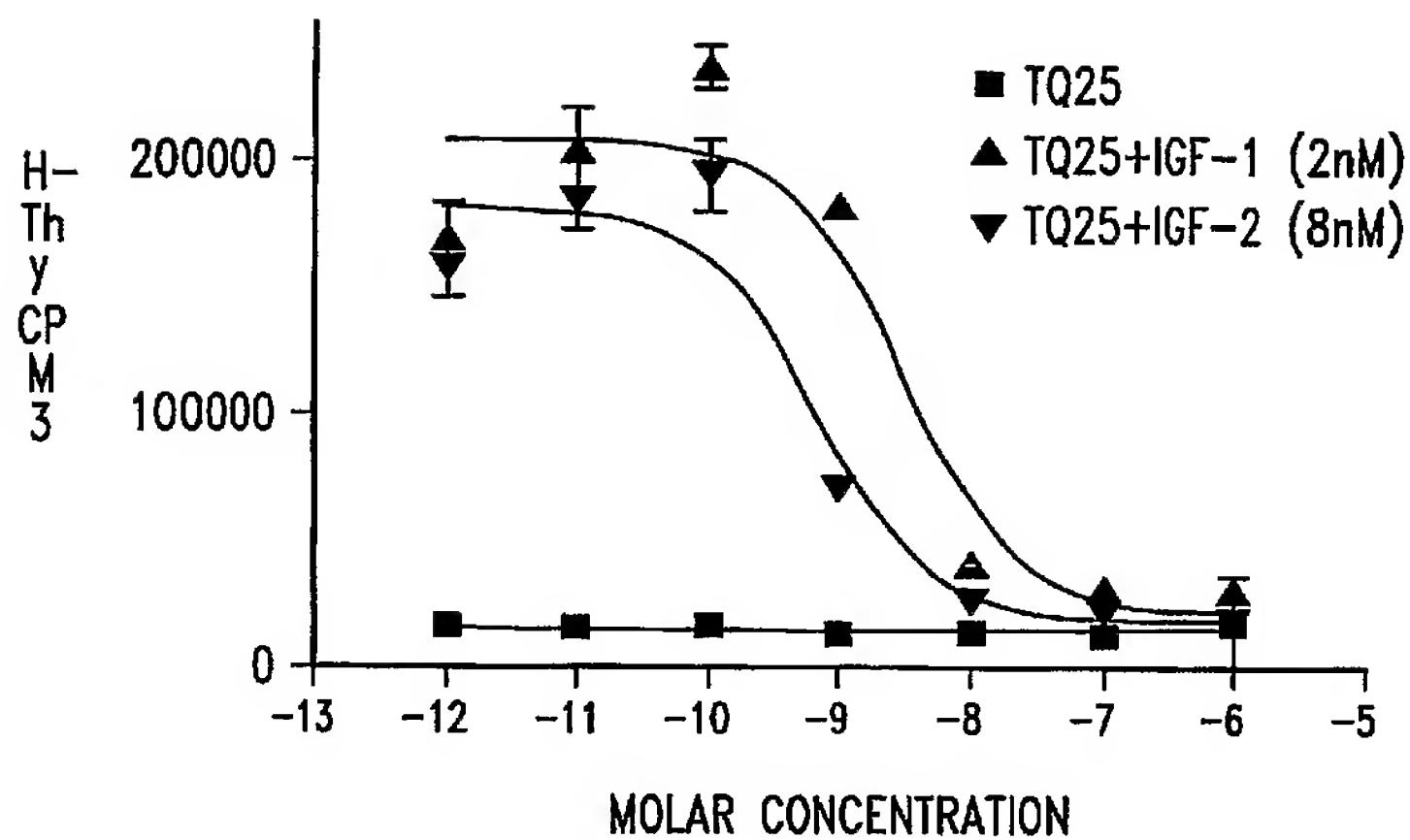
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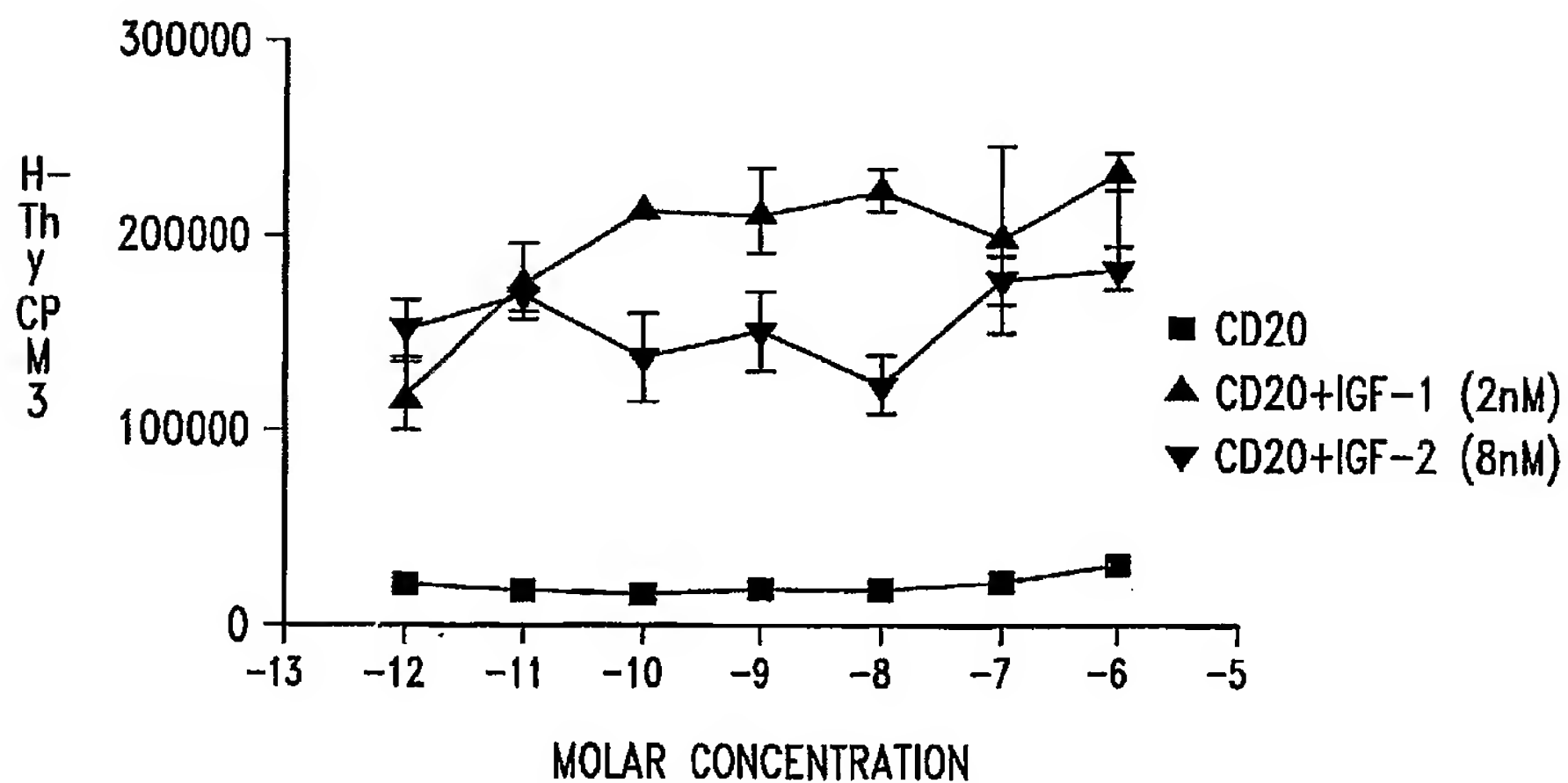
Fig. 17D

Fig. 17E

Fig. 17F

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       Tsai, Mei-Mei

<120> COMPOSITIONS AND METHODS RELATING TO ANTI IGF-1 RECEPTOR
       ANTIBODIES

<130> A-954 (WO)

<140> --to be assigned--
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gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt   96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20   25   30

agt gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct   144
Ser Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35   40   45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct   192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50   55   60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc   240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65   70   75   80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct   288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85   90   95

cta caa act ccg atc acc ttc ggc caa ggg aca cga ctg gag att aaa   336
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Ser Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35   40   45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50   55   60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65   70   75   80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
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Leu Gln Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
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1   5   10   15

tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt aat gga tac   96
Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr

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                 20                      25                      30
aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct cca cag ctc     144
Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu
        35                      40                      45

ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct gac agg ttc     192
Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe
        50                      55                      60

agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc agc aga gtg     240
Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val
65                      70                      75                  80

gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct cta caa act     288
Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln Thr
                    85                      90                      95

ccg atc acc ttc ggc caa ggg aca cga ctg gag att aaa               327
Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
                    100                     105
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Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu
            35                  40                      45


Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe
        50                  55                      60


Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val
65                  70                  75                      80


Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln Thr
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Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
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<400>   5
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct       192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc       240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct       288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act cca ctc act ttc ggc ggc ggg acc aag gtg gag atc aaa       336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
        .


<210>   6
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   6

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30
```

```
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

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<210>  7
<211>  336
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(336)

<400>  7
gaa att gtg atg acg cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt       96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct      144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct      192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc      240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct      288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act cct cac act ttc ggc gga ggg acc aag gtg gag atc aaa      336
Leu Gln Thr Pro His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 8
<211> 112
<212> PRT
<213> Artificial

<220>
<223>   Synthetic Construct

<400>   8

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1   5   10   15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20   25   30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35   40   45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50   55   60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65   70   75   80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85   90   95

Leu Gln Thr Pro His Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105   110

<210> 9
<211> 336
<212> DNA
<213> Artificial

<220>
<223>   light chain variable region

<220>
<221>   CDS
<222>   (1)..(336)

<400>   9
gaa att gtg ctg act cag tct cca ctc tcc ctg ccc gtc acc cct gga   48
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1   5   10   15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt   96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20   25   30

```
aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct        144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct        192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc        240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct        288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa acc cct ctc act ttc ggc cct ggg acc aaa gtg gat atc aaa        336
Leu Gln Thr Pro Leu Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105                 110
```

```
<210>   10
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   10

Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5           .       10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105                 110


<210>   11
```

7

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<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   11
gat gtt gtg atg act cag tct cca ctc tcc ctg gcc gtc acc cct gga        48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Ala Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct       192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc       240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct       288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act ccg ctc act ttc ggc gga ggg acc aag gtg gag atc aaa       336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>   12
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   12

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Ala Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
```

```
                35                      40                          45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
```

```
<210>   13
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   13
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt      96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct     144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct     192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc     240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct     288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


cta caa act cct ctc act ttc ggc gga ggg acc aag gtg gag atc aaa     336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
```

```
<210>   14
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   14

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110


<210>   15
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   15
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt      96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30
```

```
aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct      144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct      192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc      240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gaa gat gtt ggg gtt tat tac tgt atg caa gct      288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa acc ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa      336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

```
<210>   16
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   16
```

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

```
<210>   17
<211>   336
```

```
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   17
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt      96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct     144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct     192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc     240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct     288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act ccg ttc acc ttc ggc caa ggg aca cga ctg gag att aaa     336
Leu Gln Thr Pro Phe Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105                 110


<210>   18
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   18

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45
```

```
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60
```

```
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80
```

```
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95
```

```
Leu Gln Thr Pro Phe Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105                 110
```

```
<210>  19
<211>  336
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(336)

<400>  19
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt      96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct     144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct     192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc     240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct     288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act cct ctg gcg ttc ggc caa ggg acc aag gtg gaa atc aaa     336
Leu Gln Thr Pro Leu Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

13

```
<210>   20
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   20
```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1   5   10   15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20   25   30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35   40   45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50   55   60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65   70   75   80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
            85   90   95

Leu Gln Thr Pro Leu Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105   110

```
<210>   21
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   21
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gaa att gtg ctg act cag tct cca ctc tcc ctg ccc gtc acc cct gga   48
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1   5   10   15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt   96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20   25   30

aat gga tac aac tat ttg aat tgg tac ctg cag aag cca ggg cag tct   144

14

```
Asn Gly Tyr Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35              40              45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct        192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50              55              60

gac agg ttc agt gcc agt gga tca ggc aca gat ttt aca ctg aaa atc        240
Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct        288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
            85              90              95

cta caa act cct atc acc ttc ggc caa ggg aca cga ctg gag att aaa        336
Leu Gln Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100             105             110
```

```
<210>   22
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   22

Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5               10              15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20              25              30


Asn Gly Tyr Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35              40              45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50              55              60


Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
            85              90              95


Leu Gln Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100             105             110
```

```
<210>   23
<211>   333
<212>   DNA
```

```
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(333)

<400>   23
aat ttt atg ctg act cag ccc cac tct gtg tcg gag tct ccg ggg aag       48
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1               5                   10                  15

acg gta acc atc tcc tgc acc cgc agc agt ggc agc att gcc agc aac       96
Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
                20                  25                  30

tat gtg cag tgg tac cag cag cgc ccg ggc agt tcc ccc acc act gtg      144
Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val
            35                  40                  45

atc tat gag gat aac caa aga ccc tct ggg gtc cct gat cgg ttc tct      192
Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
        50                  55                  60

ggc tcc atc gac agc tcc tcc aac tct gcc tcc ctc acc atc tct gga      240
Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80

ctg aag act gag gac gag gct gac tac tac tgt cag tct tat gat agc      288
Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
                85                  90                  95

agc aat cag aga gtg ttc ggc gga ggg acc aag ctg acc gtc cta          333
Ser Asn Gln Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                100                 105                 110


<210>   24
<211>   111
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   24

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1               5                   10                  15


Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
                20                  25                  30


Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val
            35                  40                  45
```

```
Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60
```

```
Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80
```

```
Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
                85                  90                  95
```

```
Ser Asn Gln Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                100                 105                 110
```

```
<210>   25
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   25
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct       192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc       240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct       288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa acc ccg ctc act ttc ggc gga ggg acc aag gtg gag atc aaa       336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110


<210>   26
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<211>  112
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  26

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110


<210>  27
<211>  336
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(336)

<400>  27
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
```

18

```
              35                      40                      45
cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct    192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc    240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct    288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act cct ctt act ttc ggc gga ggg acc aag gtg gag atc aaa    336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
```

```
<210>   28
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   28

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110


<210>   29
<211>   336
<212>   DNA
<213>   Artificial
```

```
<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(336)

<400>  29
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1                 5                  10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg caa aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct tat cgg gcc tcc ggg gtc cct       192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro
        50                  55                  60

gac agg ttc agt gcc agt gga tca ggc aca gat ttt aca ctg aaa atc       240
Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct       288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act ccg atc acc ttc ggc caa ggg aca cga ctg gag att aaa       336
Leu Gln Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
                100                 105                 110


<210>  30
<211>  112
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  30

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1                 5                  10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45
```

```
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

Leu Gln Thr Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
                100                 105                 110
```

<210> 31
<211> 336
<212> DNA
<213> Artificial

<220>
<223> light chain variable region

<220>
<221> CDS
<222> (1)..(336)

<400> 31
```
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct       192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc       240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc agg gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa ggt       288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85                  90                  95

aca cac tgg cct ctg acg ttc ggc caa ggg acc aag gtg gag atc aaa       336
Thr His Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
```

<210> 32
<211> 112

```
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  32

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1                   5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70.                 75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85                  90                  95


Thr His Trp Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
                100                 105                 110


<210>  33
<211>  335
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(333)

<400>  33
gaa att gtg atg acg cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Glu Ile Val Met Thr Gln Ser Pro Leu Ser.Leu Pro Val Thr Pro Gly
1                   5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt      96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20              ·       25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct     144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45
```

```
cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct        192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc        240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct        288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act cct ctc act ttc ggc gga ggg acc aag gtg gag atc aa         335
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
                100                 105                 110
```

```
<210>   34
<211>   111
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   34
```

```
Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
                100                 105                 110
```

```
<210>   35
<211>   321
<212>   DNA
<213>   Artificial
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```
<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(321)

<400>  35
gac atc cag ttg acc cag tct cca tct tcc gtg tct gcg tct gtc gga      48
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

gac aga gtc acc atc act tgt cgg gcg agt cag ggt att agc agg tgg      96
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Arg Trp
            20                  25                  30

tta gcc tgg tat caa cag aaa cca ggg aaa gcc cct aga ctc ctg atc     144
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu Leu Ile
        35                  40                  45

tat gct gcg tcc ggt tta caa agt ggg gtc cca tca agg ttc agc ggc     192
Tyr Ala Ala Ser Gly Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

agt gga tct ggg aca gat ttc act ctc acc atc agc aac ctg cag cct     240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Leu Gln Pro
65                  70                  75                  80

gaa gat ttt gca act tac tat tgt caa cag gct agc agt ttt cca atc     288
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Ser Ser Phe Pro Ile
                85                  90                  95

acc ttc ggc caa ggg aca cga ctg gag act aaa                         321
Thr Phe Gly Gln Gly Thr Arg Leu Glu Thr Lys
            100                 105


<210>  36
<211>  107
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  36

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Arg Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Gly Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
```

```
        50                    55                    60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Ser Ser Phe Pro Ile
                85                  90                  95


Thr Phe Gly Gln Gly Thr Arg Leu Glu Thr Lys          .
            100                 105
```

```
<210>   37
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)


<400>   37
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga       48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1                   5                   10                  15


gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt       96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30


aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct      144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct      192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50                  55                  60


gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc      240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


agc aga gtg gag gct gag gat gtt gga gtt tat tac tgc atg caa gct      288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


cta caa act ccg tac act ttt ggc cag ggg acc aag ctg gag atc aaa      336
Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
                100                 105                 110


<210>   38
<211>   112
<212>   PRT
```

```
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   38

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
            85                  90                  95


Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210>   39
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   39
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45
```

```
cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct    192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50              55                  60

aac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc    240
Asn Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct    288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
            85                  90                  95

cta caa act cca ttc act ttc ggc cct ggg acc aaa gtg gat atc aaa    336
Leu Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105                 110
```

```
<210>   40
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   40
```

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asn Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105                 110
```

```
<210>   41
<211>   336
<212>   DNA
<213>   Artificial

<220>
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<223>   light chain variable region

<220>
<221>   CDS
<222>   (1)..(336)

<400>   41
```
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga          48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt          96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


cat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct          144
His Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


cca caa ctt ctg atc tat ttg ggt tct tat cgg gcc tcc ggg gtc cct          192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro
    50                  55                  60


gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc          240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa tct          288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser
                85                  90                  95


cta gaa gtt ccg ttc act ttt ggc cag ggg acc aag ctg gag atc aaa          336
Leu Glu Val Pro Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
                100                 105                 110
```


<210>   42
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   42

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15



Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30



His Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45



Pro Gln Leu Leu Ile Tyr Leu Gly Ser Tyr Arg Ala Ser Gly Val Pro
    50                  55                  60
```

```
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser
                85                  90                  95


Leu Glu Val Pro Phe Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
                100                 105                 110
```

```
<210>  43
<211>  321
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(321)

<400>  43
tct tct gag ctg act cag gac cct gct gtg tct gtg gcc ttg gga cag      48
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1               5                   10                  15

aca gtc agg atc aca tgc caa gga gac agc ctc aga att tat tat aca      96
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ile Tyr Tyr Thr
                20                  25                  30

ggc tgg tac caa cag aag cca gga cag gcc cct gtg ctt gtc ctc ttt     144
Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Leu Phe
            35                  40                  45

ggt aag aac aat cgg ccc tca ggg atc cca gac cga ttc tct ggc tcc     192
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
        50                  55                  60

cac tca ggg aac aca gct tcc ttg acc atc act ggg gct caa gcg gaa     240
His Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65                  70                  75                  80

gat gag gct gac tat tac tgt aac tcc cgg gac atc act ggt gtc cat     288
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ile Thr Gly Val His
                85                  90                  95

cga ttc ggc gga ggg acc aag ctg acc gtc cta                         321
Arg Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                100                 105
```

```
<210>  44
<211>  107
<212>  PRT
<213>  Artificial
```

```
<220>
<223>   Synthetic Construct

<400>   44

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1               5                   10                  15


Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ile Tyr Tyr Thr
            20                  25                  30


Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Leu Phe
        35                  40                  45


Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    50                  55                  60


His Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65                  70                  75                  80


Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ile Thr Gly Val His
                85                  90                  95


Arg Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210>   45
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   45
gaa att gtg ctg act cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct       192
```

```
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc    240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct    288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act cct ctc act ttc ggc gga ggg acc aag gtg gag atc aaa    336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
```

```
<210>   46
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   46
```

```
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
```

```
<210>   47
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region
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```
<220>
<221>  CDS
<222>  (1)..(336)

<400>  47
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt      96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct     144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
                35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct     192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc     240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct     288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act cct aac act ttc ggc gga ggg acc aag gtg gag atc aaa     336
Leu Gln Thr Pro Asn Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110


<210>  48
<211>  112
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  48

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
                35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50                  55                  60
```

32

```
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
            85              90              95


Leu Gln Thr Pro Asn Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        100             105             110
```

```
<210>  49
<211>  336
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(336)

<400>  49
```

```
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga    48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10              15


gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt    96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20              25              30


aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct   144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35              40              45


cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct   192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50              55              60


gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc   240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80


agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct   288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
            85              90              95


cta caa act cca atc act ttc ggc cct ggg acc aaa gtg gat atc aaa   336
Leu Gln Thr Pro Ile Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
        100             105             110
```

```
<210>  50
<211>  112
<212>  PRT
<213>  Artificial
```

```
<220>
<223>   Synthetic Construct

<400>   50
```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1   5   10   15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20   25   30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35   40   45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50   55   60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65   70   75   80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
            85   90   95

Leu Gln Thr Pro Ile Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100   105   110

```
<210>   51
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   51
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt      96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac acc tat ttg gat tgg tac ctg cag aag cca ggg cag tct     144
Asn Gly Tyr Thr Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

cca caa ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct     192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
```

```
        50                        55                        60
gac agg ttc agc ggc agt gga tca ggc aca gat ttt aca ctg aaa atc    240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag cct gag gat gtt ggg gtc tat tac tgc atg caa gct    288
Ser Arg Val Glu Pro Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta gaa atg ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa    336
Leu Glu Met Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
```

<210> 52
<211> 112
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 52

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30

Asn Gly Tyr Thr Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Pro Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

Leu Glu Met Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
```

<210> 53
<211> 321
<212> DNA
<213> Artificial

<220>
<223> light chain variable region

```
<220>
<221>  CDS
<222>  (1)..(321)

<400>  53
gac atc cag ttg acc cag tct cca tcc ttc ctg tct gca tct gta gga     48
Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15

gac aga gtc acc atc act tgc cgg gcc agt cag ggc att agc agt tat     96
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
                20                  25                  30

tta gcc tgg tat cag caa aaa cca ggg aaa gcc cct aag ctc ctg atc    144
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
            35                  40                  45

tat gct gca tcc act ttg caa agt ggg gtc cca tca agg ttc agc ggc    192
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
        50                  55                  60

agt gga tct ggg aca gaa ttc act ctc aca atc agc agc ctg cag cct    240
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

gaa gat ttt gca act tat tac tgt caa cag ctt aat agt tac ccc ctc    288
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Leu
                85                  90                  95

act ttc ggc gga ggg acc aag gtg gag atc aaa                        321
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  54
<211>  107
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  54

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
                20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
            35                  40                  45


Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
        50                  55                  60
```

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Leu
                    85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210>   55
<211>   315
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region

<220>
<221>   CDS
<222>   (1)..(315)

<400>   55
tcc tat gtg ctg act cag cca ccc tca gtg tcc gtg tcc cca gga cag   48
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1   5   10   15

aca gcc agc atc acc tgc tct gga gat aaa ttg ggg gat aaa tat gtt   96
Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val
            20   25   30

ggc tgg tat cag caa aag gca ggc caa gcc cct gtt ttg gtc atc tat   144
Gly Trp Tyr Gln Gln Lys Ala Gly Gln Ala Pro Val Leu Val Ile Tyr
        35   40   45

caa gac aac aag cga ccc tca ggg atc cct gag cga ttc tct ggc tcc   192
Gln Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50   55   60

aac tct ggg aac aca gcc agt ctg acc atc agc ggg acc cag gct atg   240
Asn Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Thr Gln Ala Met
65   70   75   80

gat gag gct gac tat tac tgt cag gcg tgg gac agc ggc acg gtg ttc   288
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Gly Thr Val Phe
                    85   90   95

ggc gga ggg acc aag ctg acc gtc cta   315
Gly Gly Gly Thr Lys Leu Thr Val Leu
            100   105

<210>   56
<211>   105
<212>   PRT
<213>   Artificial

<220>

<223>   Synthetic Construct

<400>   56

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
1   5   10   15

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys Tyr Val
.   20   25   30

Gly Trp Tyr Gln Gln Lys Ala Gly Gln Ala Pro Val Leu Val Ile Tyr
            35   40   45

Gln Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
        50   55   60

Asn Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Thr Gln Ala Met
65   70   75   80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Gly Thr Val Phe
                85   90   95

Gly Gly Gly Thr Lys Leu Thr Val Leu
            100   105

<210>   57
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region

<220>
<221>   CDS
<222>   (1)..(336)

<400>   57
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga   48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1   5   10   15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt   96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20   25   30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct   144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35   40   45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct   ·192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50   55   60

```
gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc    240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct    288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa acc ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa    336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
```

<210> 58
<211> 112
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 58

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20              25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40              45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
```

<210> 59
<211> 336
<212> DNA
<213> Artificial

<220>
<223> light chain variable region
```

```
<220>
<221>  CDS
<222>  (1)..(336)

<400>  59
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga          48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt         96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct        144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct        192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc        240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg gaa gct        288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Glu Ala
            85                  90                  95

cta caa act cca ttc act ttc ggc cct ggg acc aag gtg gaa atc aaa        336
Leu Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  60
<211>  112
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  60

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
```

```
   65                    70                    75                    80
```

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Glu Ala
                 85   90   95

Leu Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys
                100   105   110


```
<210>  61
<211>  321
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(321)

<400>  61
gac atc cag ttg acc cag tct cca tcc tcc ctg tct gcg tct gtg gga      48
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

gac aga gtc acc atc act tgc cgg tca agt caa ggc att ggt tac ttc      96
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Gly Ile Gly Tyr Phe
            20                  25                  30

tta aat tgg tat cag cag gaa cca ggg aaa gcc cca aag atc ctg atc     144
Leu Asn Trp Tyr Gln Gln Glu Pro Gly Lys Ala Pro Lys Ile Leu Ile
        35                  40                  45

tct gct gca tcc act ttg caa agt ggg gtc cca tca agg ttc agt ggc     192
Ser Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

agt gga tct ggg aca gat ttc aca ctc tcc atc aac aat ctg caa ccc     240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Asn Leu Gln Pro
65                  70                  75                  80

gca gat ttt gcg aca tac tac tgt caa cag agt cac agt ccc ccg tac     288
Ala Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser Pro Pro Tyr
                85                  90                  95

act ttc ggc cag ggg acc aag gtg gag atc aaa                         321
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
                100                 105


<210>  62
<211>  107
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct
```

<400> 62

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Gly Ile Gly Tyr Phe
                20   25   30

Leu Asn Trp Tyr Gln Gln Glu Pro Gly Lys Ala Pro Lys Ile Leu Ile
            35   40   45

Ser Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
        50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Asn Leu Gln Pro
65   70   75   80

Ala Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser Pro Pro Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210>   63
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region

<220>
<221>   CDS
<222>   (1)..(336)

<400>   63
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga   48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1   5   10   15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt   96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20   25   30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct   144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35   40   45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct   192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50   55   60

42

```
gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc   240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct   288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85              90                  95

cta caa act ccg ctc act ttc ggc gga ggg acc aag gtg gag atc aaa   336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100             105                 110
```

<210> 64
<211> 112
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 64

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20              25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35              40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50              55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85              90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100             105                 110
```

<210> 65
<211> 336
<212> DNA
<213> Artificial

<220>
<223> light chain variable region

<220>

```
<221>   CDS
<222>   (1)..(336)

<400>   65
gaa att gtg ctg act cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

cca cag ctc ctg atg tat ttg gtt tct aat cgg gcc tcc ggg gtc cct       192
Pro Gln Leu Leu Met Tyr Leu Val Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gag agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc       240
Glu Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa act       288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
                85                  90                  95

cta caa act cct ctc agt ttt ggc cag ggg acc aag ctg gag atc aaa       336
Leu Gln Thr Pro Leu Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210>   66
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   66

Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Met Tyr Leu Val Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Glu Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80
```

44

.

```
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
                85              90              95
```

```
Leu Gln Thr Pro Leu Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100             105             110
```

<210> 67
<211> 336
<212> DNA
<213> Artificial

<220>
<223> light chain variable region

<220>
<221> CDS
<222> (1)..(336)

<400> 67
```
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15
```

```
gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt      96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30
```

```
aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct     144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45
```

```
cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct     192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60
```

```
gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc     240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80
```

```
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct     288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85              90              95
```

```
cta caa act ccg ctc act ttc ggc gga ggg acc aag gtg gag atc aaa     336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100             105             110
```

<210> 68
<211> 112
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400>   68

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1   5   10   15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20   25   30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35   40   45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50   55   60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65   70   75   80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85   90   95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105   110

<210>   69
<211>   330
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region

<220>
<221>   CDS
<222>   (1)..(330)

<400>   69
aat ttt atg ctg act cag ccc cac tct gtg tcg gcg tct ccg ggg aag   48
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Ala Ser Pro Gly Lys
1   5   10   15

acg gtt acc atc tcc tgc acc cgc agc agt ggc gac att gac aac aac   96
Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Asp Ile Asp Asn Asn
            20   25   30

tat gtg cag tgg tac cag cag cgc ccg ggc aat tcc ccc acc aat gtg   144
Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Asn Ser Pro Thr Asn Val
        35   40   45

att tat gag gat aac cga aga ccc tct ggg gtc ccg gat cgc ttc tct   192
Ile Tyr Glu Asp Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50   55   60

ggc tcc atc gac agc tcc tcc aac tct gcc tcc ctc acc atc tct gga   240

46

```
Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80

ctg cag cct gag gac gag gct gac tac tat tgt cag tct tat caa agc        288
Leu Gln Pro Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Gln Ser
                85                  90                  95

gac aat tgg gtg ttc ggc gga ggg acc aag gtg acc gtc cta              330
Asp Asn Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 70
<211> 110
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 70

```
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Ala Ser Pro Gly Lys
1               5                   10                  15


Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Asp Ile Asp Asn Asn
                20                  25                  30


Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Asn Ser Pro Thr Asn Val
            35                  40                  45


Ile Tyr Glu Asp Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60


Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80


Leu Gln Pro Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Gln Ser
                85                  90                  95


Asp Asn Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 71
<211> 330
<212> DNA
<213> Artificial

<220>
<223> light chain variable region

<220>
<221> CDS
```

```
<222>   (1)..(330)

<400>   71
aat ttt atg ctg act cag ccc cac tct gtg tcg gag tct ccg ggg aag      48
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1               5               10              15

acg gta acc atc tcc tgc acc cgc agc agt ggc agc att gcc agc aac      96
Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
                20              25              .30

tat gtg cag tgg tac cag cag cgc ccg ggc agt tcc ccc acc act gtg     144
Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val
            35              40              45

atc tat gag gat aac caa aga ccc tct ggg gtc cct gat cga ttc tct     192
Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
        50              55              60

ggc tcc atc gac agc tcc tcc aac tct gcc tcc ctc acc atc tct gga     240
Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65              70              75              80

ctg aag act gag gac gag gct gac tac tac tgt cag tct tat gat agc     288
Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
                85              90              95

agc aat gtg gtg ttc ggc gga ggg acc aag ctg acc gtc cta             330
Ser Asn Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100             105             110


<210>   72
<211>   110
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   72

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1               5               10              15


Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
                20              25              30


Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val
            35              40              45


Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
        50              55              60


Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65              70              75              80
```

```
Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
                 85                  90                  95
```

```
Ser Asn Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                100                 105                 110
```

<210> 73
<211> 336
<212> DNA
<213> Artificial

<220>
<223> light chain variable region

<220>
<221> CDS
<222> (1)..(336)

<400> 73
```
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct ggg     48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15
```

```
gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt     96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30
```

```
aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct    144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45
```

```
cca cag ctc ctg atc tat ttg ggt tct aac cgg gac tct ggg gtc cca    192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Asp Ser Gly Val Pro
    50                  55                  60
```

```
gac aga ttc agc ggc agt ggg tca ggc act gat ttc aca ctg aaa atc    240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80
```

```
agc agg gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa ggt    288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85                  90                  95
```

```
aca cac tgg ccg tac act ttt ggc cag ggg acc agg ctg gag atc aaa    336
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
                100                 105                 110
```

<210> 74
<211> 112
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 74

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Asp Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
                85                  90                  95


Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
                100                 105                 110
```

```
<210>   75
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   75
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag tcg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt      96
Glu Ser Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac ttt ttg gat tgg tac ctg cag aag cca ggg cag tct     144
Asn Gly Tyr Asn Phe Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct     192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc     240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
```

```
65                      70                    75                    80
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct    288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                    85                    90                    95

cta caa act cct ctc act ttc ggc gga ggg acc aag gtg gag atc aaa    336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                   105                   110
```

<210> 76
<211> 112
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 76

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Ser Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Phe Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
            85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 77
<211> 336
<212> DNA
<213> Artificial

<220>
<223> light chain variable region

<220>
<221> CDS
<222> (1)..(336)

```
<400>  77
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga    48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5               10              15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt    96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20              25              30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct   144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35              40              45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct   192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50              55              60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc   240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct   288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85              90              95

cta caa acc ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa   336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100             105             110
```

```
<210>  78
<211>  112
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  78
```

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5               10              15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20              25              30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35              40              45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50              55              60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80
```

```
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
             85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
             100                 105                 110
```

```
<210>  79
<211>  321
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(321)

<400>  79
gaa acg aca ctc acg cag tct cca gcc acc ctg tct ttg tct cca ggg     48
Glu Thr Thr Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

caa aga gcc acc ctc tcc tgc agg gcc agt cag agt gtc tac aac tac     96
Gln Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Tyr Asn Tyr
            20                  25                  30

tta gcc tgg tac caa cag aag cct ggc cag gct ccc agg ctc ctc atc    144
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

tat gat gca tcc aga agg gca act ggc atc cca gcc agg ttc agt ggc    192
Tyr Asp Ala Ser Arg Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

agt ggg tct ggg aca gac ttc act ctc acc atc agc agc cta gag cct    240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

gaa gat ttt gca gtt tat tac tgt cag cag cgt aac aac tgg ccg ctc    288
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn Asn Trp Pro Leu
                85                  90                  95

act ttc ggt gga ggg acc aag gtg gag atc aaa                        321
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105


<210>  80
<211>  107
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  80
```

53

```
Glu Thr Thr Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Gln Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Tyr Asn Tyr
                20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
            35                  40                  45

Tyr Asp Ala Ser Arg Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
        50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Asn Asn Trp Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

```
<210>   81
<211>   321
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(321)

<400>   81
gac atc cag ttg acc cag tct cca tcc tcc ctg tct gct tct gtt gga      48
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

gac agc gtc acc atc tct tgc cgg gca agt cag agt cct ggc atc ttt      96
Asp Ser Val Thr Ile Ser Cys Arg Ala Ser Gln Ser Pro Gly Ile Phe
                20                  25                  30

tta aat tgg tat cag cag ata cca ggg aaa gcc cct aaa ctc ctg atc     144
Leu Asn Trp Tyr Gln Gln Ile Pro Gly Lys Ala Pro Lys Leu Leu Ile
            35                  40                  45

tac gct aca tcc act ctg gaa agt ggg gtc ccc ccc agg ttc acc ggc     192
Tyr Ala Thr Ser Thr Leu Glu Ser Gly Val Pro Pro Arg Phe Thr Gly
        50                  55                  60

agt gga tct ggg aca gat ttc act ctc acc atc agc agt ctg caa cct     240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
```

54

```
gag gac ttt gca act tac tac tgt caa cag agt aac agt gtt ccg ctc          288
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Ser Val Pro Leu
            85                  90                  95

act ttc ggc ggc ggg acc aag gtg gag atc aaa                              321
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100             105
```

<210> 82
<211> 107
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 82

```
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Ser Val Thr Ile Ser Cys Arg Ala Ser Gln Ser Pro Gly Ile Phe
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Ile Pro Gly Lys Ala Pro Lys Leu Leu Ile
            35                  40                  45


Tyr Ala Thr Ser Thr Leu Glu Ser Gly Val Pro Pro Arg Phe Thr Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Ser Val Pro Leu
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100             105
```

<210> 83
<211> 336
<212> DNA
<213> Artificial

<220>
<223> light chain variable region

<220>
<221> CDS
<222> (1)..(336)

<400> 83
```
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct       192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca cta aaa atc       240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct       288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act cct cta acc ttc ggc caa ggg aca cga ctg gag att aaa       336
Leu Gln Thr Pro Leu Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105                 110
```

<210> 84
<211> 112
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 84

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
        50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
```

```
                  85                    90                    95


Leu Gln Thr Pro Leu Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105                 110
```

```
<210>  85
<211>  321
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(321)

<400>  85
gaa att gtg atg acg cag tct cca gcc acc ctg tct gtg tct cca ggg      48
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15

gaa aga gcc acc ttc tcc tgt agg gcc agt cag agt gtt ggc agc aac      96
Glu Arg Ala Thr Phe Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Asn
            20                  25                  30

tta gcc tgg tac cag cag aaa cct ggc cag gct ccc agg ctc ctc atc     144
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

tat gat gca tcc aac agg gcc act ggc atc cca gcc agg ttc agt ggc     192
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

agt ggg tct ggg aca gac ttc act ctc acc atc agc aga ctg gag cct     240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65                  70                  75                  80

gaa gat ttt gca gtg tat tac tgt cag cag cgt agc aac tgg ccc ctc     288
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
                85                  90                  95

act ttc ggc gga ggg acc aag gtg gag atc aaa                         321
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105



<210>  86
<211>  107
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  86

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
```

```
1                   5                         10                        15


Glu Arg Ala Thr Phe Ser Cys Arg Ala Ser Gln Ser Val Gly Ser Asn
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

```
<210>    87
<211>    336
<212>    DNA
<213>    Artificial

<220>
<223>    light chain variable region


<220>
<221>    CDS
<222>    (1)..(336)

<400>    87
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1                   5                         10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct       192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc       240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80
```

```
agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct      288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act ccg ctc act ttc ggc gga ggg acc aag gtg gag atc aaa      336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 88
<211> 112
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 88

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 89
<211> 336
<212> DNA
<213> Artificial

<220>
<223> light chain variable region

<220>
<221> CDS
<222> (1)..(336)

<400> 89

```
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga        48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly .
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt        96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct       144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

cca cag ctc ctg atc tac ttg ggt tct act cgg gcc tcc ggc gtc cct       192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro
        50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc       240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct       288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act cct tac act ttc ggc gga ggg acc aag gtg gag atc aaa       336
Leu Gln Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                100                 105                 110
```

```
<210>   90
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   90
```

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro
        50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95
```

```
Leu Gln Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 91
<211> 336
<212> DNA
<213> Artificial

<220>
<223> light chain variable region

<220>
<221> CDS
<222> (1)..(336)

```
<400>  91
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt      96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct     144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct     192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc     240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct     288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

cta caa act ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa     336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 92
<211> 112
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 92

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15
```

```
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
            85                  90                  95

Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

```
<210>   93
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   93
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1                   5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat act      96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Thr
            20                  25                  30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct     144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45

cca cgg ctc ctg atc tat ttg ggt ttt aat cgg gcc tcc ggg gtc cct     192
Pro Arg Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro
    50                  55                  60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc     240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgt atg caa ggt     288
```

```
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
              85                  90                  95

cta caa act ccc ctc act ttc ggc gga ggg acc aag gtg gag atc aaa       336
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

```
<210>  94
<211>  112
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  94
```

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1              5                  10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Thr
              20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
            35                  40                  45


Pro Arg Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro
       50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
              85                  90                  95


Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

```
<210>  95
<211>  336
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(336)

<400>  95
gat gtt gtg atg act cag tct cca ctc tcc ctg ccc gtc acc cct gga       48
```

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5               10              15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat agt    96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20              25              30

aat gga tac aac tat ttg gat tgg tac ctg cag aag cca ggg cag tct    144
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35              40              45

cca cag ctc ctg atc tat ttg ggt tct aat cgg gcc tcc ggg gtc cct    192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50              55              60

gac agg ttc agt ggc agt gga tca ggc aca gat ttt aca ctg aaa atc    240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80

agc agg gtg gag gct gag gat gtt ggg gtt tat tat tgc atg caa gct    288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85              90              95

aca cac tgg ccg tac act ttt ggc cag ggg acc aag ctg gag atc aaa    336
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
                100             105             110


<210>  96
<211>  112
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  96

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5               10              15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20              25              30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35              40              45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50              55              60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85              90              95
```

64

```
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110
```

```
<210>  97
<211>  330
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(330)

<400>  97
aat ttt atg ctg act cag ccc cac tct gtg tcg gag tct ccg ggg aag     48
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1               5                   10                  15

acg gta agc atc tcc tgc acc cgc aac agt ggc agc att gcc agc aac     96
Thr Val Ser Ile Ser Cys Thr Arg Asn Ser Gly Ser Ile Ala Ser Asn
                20                  25                  30

ttt gtg cag tgg tac cag cag cgc ccg ggc agt gcc ccc acc att gta    144
Phe Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Ile Val
            35                  40                  45

atc tat gag gat aac caa aga ccc tct gcg gtc cct act cgg ttc tct    192
Ile Tyr Glu Asp Asn Gln Arg Pro Ser Ala Val Pro Thr Arg Phe Ser
        50                  55                  60

ggc tcc atc gac agg tcc tcc aac tct gcc tcc ctc acc atc tct gga    240
Gly Ser Ile Asp Arg Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80

ctg acg act gag gac gag gct gac tac tac tgt cag tct tat gat agc    288
Leu Thr Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
                85                  90                  95

gcc aat gtc att ttc ggc ggg ggg acc aag ctg acc gtc cta          330
Ala Asn Val Ile Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
                .
```

```
<210>  98
<211>  110
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  98

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1               5                   10                  15
```

```
Thr Val Ser Ile Ser Cys Thr Arg Asn Ser Gly Ser Ile Ala Ser Asn
             20                  25                  30


Phe Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Thr Ile Val
         35                  40                  45


Ile Tyr Glu Asp Asn Gln Arg Pro Ser Ala Val Pro Thr Arg Phe Ser
     50                  55                  60


Gly Ser Ile Asp Arg Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80


Leu Thr Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
             85                  90                  95


Ala Asn Val Ile Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
             100                 105                 110
```

```
<210>  99
<211>  324
<212>  DNA
<213>  Artificial

<220>
<223>  light chain variable region


<220>
<221>  CDS
<222>  (1)..(324)

<400>  99
gaa acg aca ctc acg cag tct cca ggc acc ctg tct ttg tct cca ggg      48
Glu Thr Thr Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1                   5                   10                  15

gag aga gcc acc ctc tcc tgc agg gcc agt cag act atc agc agc agc      96
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Ile Ser Ser Ser
             20                  25                  30

cac tta gcc tgg tac cag cag aaa cct ggc cag tct ccc agg ctc ctc     144
His Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Arg Leu Leu
         35                  40                  45

atc tat ggt gcg ggc tac agg gcc acc ggc att cca gac agg ttc agt     192
Ile Tyr Gly Ala Gly Tyr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
     50                  55                  60

ggc agt ggg tct ggc aca gac ttc act ctc acc atc agc aga ctg gag     240
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80

cct gaa gat ttt gca gtg tat tac tgt cag cac tat ggt agt tca ctc     288
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ser Ser Leu
```

```
                    85                    90                    95
cgg acg ttc ggc caa ggg acc aag gtg gaa atc aaa                          324
Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                   105
```

<210> 100
<211> 108
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 100

```
Glu Thr Thr Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Ile Ser Ser Ser
            20                  25                  30


His Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Arg Leu Leu
        35                  40                  45


Ile Tyr Gly Ala Gly Tyr Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65                  70                  75                  80


Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Gly Ser Ser Leu
                85                  90                  95


Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                   105
```

<210> 101
<211> 330
<212> DNA
<213> Artificial

<220>
<223> light chain variable region

<220>
<221> CDS
<222> (1)..(330)

<400> 101

```
aat ttt atg ctg act cag ccc cac tct gtg tcg gag tct ccg ggg aag      48
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
```

```
1                   5                        10                        15

acg gta acc atc tcc tgc acc ggc agc ggt ggc aac att gcc agc aat          96
Thr Val Thr Ile Ser Cys Thr Gly Ser Gly Gly Asn Ile Ala Ser Asn
            20                  25                  30

tat gtg cag tgg tac cag cag cgc ccg ggc agg gcc ccc acc act gtg         144
Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Arg Ala Pro Thr Thr Val
        35                  40                  45

atc tat gag gat aat cga aga ccc tct ggg gtc cct gat cgg ttc tct         192
Ile Tyr Glu Asp Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
        50                  55                  60

ggc tcc atc gac agc tcc tcc aac tct gcc tcc ctc acc atc tct gga         240
Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80

ctg aag act gaa gac gag gct gac tac tac tgt cag tct tat gat ccc         288
Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Pro
                85                  90                  95

tac aat cga gtg ttc ggc gga ggg acc aag ctg acc gtc cta                 330
Tyr Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 102
<211> 110
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 102

```
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1               5                   10                  15


Thr Val Thr Ile Ser Cys Thr Gly Ser Gly Gly Asn Ile Ala Ser Asn
            20                  25                  30


Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Arg Ala Pro Thr Thr Val
        35                  40                  45


Ile Tyr Glu Asp Asn Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
        50                  55                  60


Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80


Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Pro
                85                  90                  95
```

```
Tyr Asn Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210>   103
<211>   336
<212>   DNA
<213>   Artificial

<220>
<223>   light chain variable region


<220>
<221>   CDS
<222>   (1)..(336)

<400>   103
gaa att gtg atg acg cag tct cca ctc tcc ctg ccc gtc acc cct gga      48
Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

gag ccg gcc tcc atc tcc tgc agg tct agt cag agc ctc ctg cat act     96
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Thr
                20                  25                  30

aat gga tac gac tat ttg gat tgg tac ctg cag aag cca ggg cag tct    144
Asn Gly Tyr Asp Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
                35                  40                  45

cca cag ctt ctg atc tat ttg ggt tct act cgg gcc tcc ggg gtc cct    192
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro
        50                  55                  60

gac agg ttc agt ggc agt gga tcg ggc aca gat ttt aca ctg aaa atc    240
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

agc aga gtg gag gct gag gat gtt ggg gtt tat tac tgc atg caa gct    288
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95

ttt caa act ccg ctc act ttc ggc gga ggg acc aag atg gag atc aaa    336
Phe Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Met Glu Ile Lys
                100                 105                 110


<210>   104
<211>   112
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   104

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15
```

```
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Thr
            20              25              30


Asn Gly Tyr Asp Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35              40              45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro
    50              55              60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
            85              90              95


Phe Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Met Glu Ile Lys
            100             105             110
```

<210> 105
<211> 351
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(351)

<400> 105
```
gag gtg cag ctg gtg gag acc ggc cca gga ctg gtg aag cct tcg ggg   48
Glu Val Gln Leu Val Glu Thr Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5               10              15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt   96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg   144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc   192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc   240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt   288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85              90              95
```

```
gcg aga ttt aat tac tat gat agt agt gtc tgg ggc cag gga acc ctg        336
Ala Arg Phe Asn Tyr Tyr Asp Ser Ser Val Trp Gly Gln Gly Thr Leu
            100             105                 110

gtc acc gtc tca agc                                                    351
Val Thr Val Ser Ser
        115
```

```
<210>   106
<211>   117
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   106
```

```
Glu Val Gln Leu Val Glu Thr Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5               10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85                  90                  95


Ala Arg Phe Asn Tyr Tyr Asp Ser Ser Val Trp Gly Gln Gly Thr Leu
            100             105                 110


Val Thr Val Ser Ser
        115
```

```
<210>   107
<211>   348
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region
```

```
<220>
<221>  CDS
<222>  (1)..(348)

<400>  107
gag gtg cag ctg gtg gag acc ggc cca gga ctg gtg aag cct tcg ggg    48
Glu Val Gln Leu Val Glu Thr Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt    96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg   144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc   192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc   240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt   288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga ggg gtt gag cag att gac tac tgg ggc cag gga acc ctg gtc   336
Ala Arg Gly Val Glu Gln Ile Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

acc gtc tca agc                                                    348
Thr Val Ser Ser
        115


<210>  108
<211>  116
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  108

Glu Val Gln Leu Val Glu Thr Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
```

```
      50                        55                        60
```

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65   70   75   80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Val Glu Gln Ile Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100   105   110

Thr Val Ser Ser
        115   .

<210>   109
<211>   354
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region

<220>
<221>   CDS
<222>   (1)..(354)

<400>   109
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg   48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt   96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20   25   30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg   144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35   40   45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc   192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
        50   55   60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc   240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65   70   75   80

ctg aag ctg agc tct gtg act gcc gcg gac acg gcc gtg tat tac tgt   288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

gcg aaa aat tta gca gca ggg gcg gtt gcc tac tgg ggc cag ggc acc   336
Ala Lys Asn Leu Ala Ala Gly Ala Val Ala Tyr Trp Gly Gln Gly Thr
            100   105   110

```
ctg gtc acc gtc tca agc                                      354
Leu Val Thr Val Ser Ser
        115


<210>  110
<211>  118
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  110

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1                   5                  10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Lys Asn Leu Ala Ala Gly Ala Val Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115


<210>  111
<211>  351
<212>  DNA
<213>  Artificial

<220>
<223>  heavy chain variable region


<220>
<221>  CDS
<222>  (1)..(351)

<400>  111
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```
cag gtg cag cta cag cag tgg ggc gca gga ctg ttg aag cct tcg gag    48
Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1               5               10              15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggg tcc ttc agt ggt tac    96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Phe Ser Gly Tyr
            20              25              30

tac tgg agc tgg atc cgt cag ccc cca ggg aag ggg ctg gag tgg att   144
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35              40              45

ggg gaa atc aat cat agt gga agt acc aac tac aac cgg tcc ctc aag   192
Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Arg Ser Leu Lys
    50              55              60

agt cga gtc acc ata tca gta gac acg tcc aag aac cag ttc tcc ctg   240
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65              70              75              80

aag ctg agc tct gtg acc gcc gcg gac acg gct gtg tat tac tgt gcg   288
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
            85              90              95

aga ctt tca tat ggt tcg ggc gtt gac tac tgg ggc cag ggc acc ctg   336
Arg Leu Ser Tyr Gly Ser Gly Val Asp Tyr Trp Gly Gln Gly Thr Leu
            100             105             110

gtc acc gtc tca agc                                                351
Val Thr Val Ser Ser
            115
```

```
<210>  112
<211>  117
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  112
```

```
Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1               5               10              15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Phe Ser Gly Tyr
            20              25              30


Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35              40              45


Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Arg Ser Leu Lys
    50              55              60


Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65              70              75              80
```

```
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                  85              90              95
```

```
Arg Leu Ser Tyr Gly Ser Gly Val Asp Tyr Trp Gly Gln Gly Thr Leu
              100              105              110
```

```
Val Thr Val Ser Ser
        115
```

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<210>   113
<211>   360
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region


<220>
<221>   CDS
<222>   (1)..(360)


<400>   113
cag ctg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tca cag      48
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5               10              15

acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85              90              95

gcg agg tat agc agc agc cgc aat gat gct ttt gat atc tgg ggc caa     336
Ala Arg Tyr Ser Ser Ser Arg Asn Asp Ala Phe Asp Ile Trp Gly Gln
            100              105              110

ggg aca atg gtc acc gtc tca agc                                      360
Gly Thr Met Val Thr Val Ser Ser
        115              120
```

```
<210>  114
<211>  120
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  114

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Tyr Ser Ser Ser Arg Asn Asp Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110


Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210>  115
<211>  354
<212>  DNA
<213>  Artificial

<220>
<223>  heavy chain variable region


<220>
<221>  CDS
<222>  (1)..(354)

<400>  115
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg      48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
```

```
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg      144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc      192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc      240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt      288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85              90              95

gcg aga gat ggg cag ctg gat gct ttt gat atc tgg ggc caa ggg aca      336
Ala Arg Asp Gly Gln Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100             105             110

atg gtc acc gtc tca agc                                              354
Met Val Thr Val Ser Ser
            115
```

```
<210>   116
<211>   118
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   116
```

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5               10              15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85              90              95
```

```
Ala Arg Asp Gly Gln Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110


Met Val Thr Val Ser Ser
        115
```

```
<210>  117
<211>  354
<212>  DNA
<213>  Artificial

<220>
<223>  heavy chain variable region


<220>
<221>  CDS
<222>  (1)..(354)


<400>  117
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg      48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga ttt tgg gac tac tac ggt atg gac gtc tgg ggc caa ggg acc     336
Ala Arg Phe Trp Asp Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
            100                 105                 110

acg gtc acc gtc tca agc                                             354
Thr Val Thr Val Ser Ser
        115


<210>  118
<211>  118
<212>  PRT
<213>  Artificial
```

<220>
<223>   Synthetic Construct

<400>   118

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20   25   30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35   40   45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65   70   75   80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85   90   95

Ala Arg Phe Trp Asp Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
            100   105   110

Thr Val Thr Val Ser Ser
        115

<210>   119
<211>   351
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region

<220>
<221>   CDS
<222>   (1)..(351)

<400>   119
cag gtg cag cta cag cag tgg ggc cca gga ctg gtg aag cct tcg ggg   48
Gln Val Gln Leu Gln Gln Trp Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt   96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20   25   30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg   144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp

```
           35                        40                        45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc        192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                      55                      60

gag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc        240
Glu Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                      70                      75                  80

ctg aag ctg agc tct gtg acc gcc gca gac acg gcc gtg tat tac tgt        288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                      90                      95

gcg aga gat cgg tac tac ggt atg gac gtc tgg ggc caa ggg acc acg        336
Ala Arg Asp Arg Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
            100                     105                     110

gtc acc gtc tca agc                                                    351
Val Thr Val Ser Ser
            115


<210>   120
<211>   117
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   120

Gln Val Gln Leu Gln Gln Trp Gly Pro Gly Leu Val Lys Pro Ser Gly
1                   5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Glu Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Arg Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
            100                 105                 110
```

Val Thr Val Ser Ser
        115

<210>   121
<211>   354
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region

<220>
<221>   CDS
<222>   (1)..(354)

<400>   121
gag gtg cag ctg gtc gag tct ggc cca gga ctg gtg aag cct tcg ggg   48
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt   96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20   25   30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg   144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35   40   45

att ggg tac atc tat tat agt ggg agc acc tac tac aac ccg tcc ctc   192
Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu
        50   55   60

aag agt cga gtc acc atg tca gta gac acg tcc aag aac cag ttc tcc   240
Lys Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65   70   75   80

ctg aag ctg agc tct gtg acc gcc gca gac acg gcc gtg tat tac tgt   288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

gcg aga tgg agc tac ttg gat gct ttt gat atc tgg ggc caa ggg aca   336
Ala Arg Trp Ser Tyr Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100   105   110

atg gtc acc gtc tca agc   354
Met Val Thr Val Ser Ser
            115

<210>   122
<211>   118
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   122

```
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1                   5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Trp Ser Tyr Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110


Met Val Thr Val Ser Ser
            115
```

```
<210>   123
<211>   354
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region


<220>
<221>   CDS
<222>   (1)..(354)

<400>   123
gag gtg cag ctg gtg gag tct ggc cca gga ctg gtg aag cct tcg ggg       48
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1                   5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60
```

```
aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc       240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt       288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85              90              95

gcg aga gat tac gat att ttc ggt atg gac gtc tgg ggc caa ggg acc       336
Ala Arg Asp Tyr Asp Ile Phe Gly Met Asp Val Trp Gly Gln Gly Thr
            100             105             110

acg gtc acc gtc tca agc                                               354
Thr Val Thr Val Ser Ser
        115
```

<210> 124
<211> 118
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 124

```
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5               10              15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85              90              95


Ala Arg Asp Tyr Asp Ile Phe Gly Met Asp Val Trp Gly Gln Gly Thr
            100             105             110


Thr Val Thr Val Ser Ser
        115
```

<210> 125

84

```
<211>   354
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region


<220>
<221>   CDS
<222>   (1)..(354)

<400>   125
cag ctg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg      48
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag tcc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Ser Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga gcc aac aga gat gat gct ttt gat atc tgg ggc caa ggg aca     336
Ala Arg Ala Asn Arg Asp Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110

atg gtc acc gtc tca agc                                             354
Met Val Thr Val Ser Ser
            115


<210>   126
<211>   118
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   126

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
```

```
              20                      25                      30
```

```
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45
```

```
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60
```

```
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Ser Ser
65                  70                  75                  80
```

```
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Ala Asn Arg Asp Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110
```

```
Met Val Thr Val Ser Ser
        115
```

```
<210>  127
<211>  357
<212>  DNA
<213>  Artificial
```

```
<220>
<223>  heavy chain variable region
```

```
<220>
<221>  CDS
<222>  (1)..(357)
```

```
<400>  127
gag gtg cag ctg gtg gag tct ggg gga ggc ttg gta cag ccg ggg ggg      48
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1                   5                   10                  15
```

```
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttt agc agc tat      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
                20                  25                  30
```

```
gcc atg agc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc     144
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
tca gct att agt ggt agt ggt ggt agc aca tac tac gca gac tcc gtg     192
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
```

```
aag ggc cgg ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat     240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
```

```
ctg caa atg aac agt ctg agc gcc gac gac acg gcc gta tat ttc tgt       288
Leu Gln Met Asn Ser Leu Ser Ala Asp Asp Thr Ala Val Tyr Phe Cys
                85                      90                  95

gcg tcg ggt ggc tgg tac ggg gac tac ttt gac tac tgg ggc cag gga       336
Ala Ser Gly Gly Trp Tyr Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

acc ctg gtc acc gtc tca agc                                           357
Thr Leu Val Thr Val Ser Ser
        115
```

```
<210>   128
<211>   119
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   128
```

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Ser Ala Asp Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95


Ala Ser Gly Gly Trp Tyr Gly Asp Tyr Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser
        115
```

```
<210>   129
<211>   363
<212>   DNA
<213>   Artificial

<220>
```

<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(363)

<400> 129
```
cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg gag      48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1                   5                  10                  15

acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga gaa ggg aac cga acg gtg act agt gct ttt gat atc tgg ggc     336
Ala Arg Glu Gly Asn Arg Thr Val Thr Ser Ala Phe Asp Ile Trp Gly
            100                 105                 110

caa ggg aca atg gtc acc gtc tca agc                                 363
Gln Gly Thr Met Val Thr Val Ser Ser
            115                 120
```


<210> 130
<211> 121
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 130

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1                   5                  10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45
```

```
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60
```

```
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80
```

```
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Glu Gly Asn Arg Thr Val Thr Ser Ala Phe Asp Ile Trp Gly
            100                 105                 110
```

```
Gln Gly Thr Met Val Thr Val Ser Ser
            115                 120
```

```
<210>  131
<211>  357
<212>  DNA
<213>  Artificial

<220>
<223>  heavy chain variable region


<220>
<221>  CDS
<222>  (1)..(357)

<400>  131
cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg      48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                  10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
                35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tac tac tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga ggg ctg ggg gat agt agt ggt tat atc ctt tgg ggc caa ggg     336
```

Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly
            100   105   110

aca atg gtc acc gtc tca agc   357
Thr Met Val Thr Val Ser Ser
            115

<210>   132
<211>   119
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   132

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20   25   30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35   40   45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65   70   75   80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly
            100   105   110

Thr Met Val Thr Val Ser Ser
            115

<210>   133
<211>   357
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region

<220>
<221>   CDS

<222> (1)..(357)

<400> 133
```
cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg      48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tac tac tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga ggg ctg ggg gat agt agt ggt tat atc ctt tgg ggc caa ggg     336
Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly
            100                 105                 110

aca atg gtc acc gtc tca agc                                         357
Thr Met Val Thr Val Ser Ser
        115
```

<210> 134
<211> 119
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 134

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60
```

```
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70              75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85              90                  95


Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly
            100             105             110


Thr Met Val Thr Val Ser Ser
        115
```

```
<210>   135
<211>   357
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region


<220>
<221>   CDS
<222>   (1)..(357)


<400>   135
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg      48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1                 5               10                  15


acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25                  30


aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40                  45


att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55                  60


aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70              75                  80


ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85              90                  95


gcg aga tgg acc ggg cgt act gat gct ttt gat atc tgg ggc caa ggg     336
Ala Arg Trp Thr Gly Arg Thr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100             105             110


aca atg gtc acc gtc tca agc                                         357
Thr Met Val Thr Val Ser Ser
```

115

<210> 136
<211> 119
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 136

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20   25   30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35   40   45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65   70   75   80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85   90   95

Ala Arg Trp Thr Gly Arg Thr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100   105   110

Thr Met Val Thr Val Ser Ser
            115

<210> 137
<211> 354
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(354)

<400> 137
cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg   48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly

```
1                    5                        10                        15
acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt        96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg       144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc       192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc       240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                      70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt       288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga caa ggg gcg tta gat gct ttt gat atc tgg ggc caa ggg acc       336
Ala Arg Gln Gly Ala Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110

acg gtc acc gtc tca agc                                               354
Thr Val Thr Val Ser Ser
            115
```

```
<210>    138
<211>    118
<212>    PRT
<213>    Artificial

<220>
<223>    Synthetic Construct

<400>    138
```

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1                    5                        10                        15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                      70                  75                  80
```

94

```
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                  85                  90                  95


Ala Arg Gln Gly Ala Leu Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110


Thr Val Thr Val Ser Ser
        115
```

<210> 139
<211> 366
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(366)

<400> 139

```
cag gtg cag ctg gtg gag tcc ggg gga ggc gtg gtc cga cct ggg ggg       48
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1               5                   10                  15


tcc ctg aga ctc tcc tgt gca gcg tct gga ttc acc ttt agc agc tat      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
                20                  25                  30


gcc atg agc tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtc     144
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
            35                  40                  45


tca act att agt ggt agt ggt ggt agc aca tac tac gca gac tcc gtg     192
Ser Thr Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
        50                  55                  60


aag ggc cgg ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat     240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


ctg cag atg aac agc ctg aga gcc gag gac acg gcc gta tat tac tgt     288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


gcg aaa gag cgt ggc agt ggc tgg tcc tta gac aat atg gac gtc tgg     336
Ala Lys Glu Arg Gly Ser Gly Trp Ser Leu Asp Asn Met Asp Val Trp
            100                 105                 110


ggc caa ggg acc acg gtc acc gtc tca agc                             366
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            115                 120
```


<210> 140
<211> 122

<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   140

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
            35   40   45

Ser Thr Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
        50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Lys Glu Arg Gly Ser Gly Trp Ser Leu Asp Asn Met Asp Val Trp
            100   105   110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            115   120

<210>   141
<211>   357
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region

<220>
<221>   CDS
<222>   (1)..(357)

<400>   141
cag gtg cag ctg gtg gag tct ggc cca gga ctg gtg aag cct tcg ggg   48
Gln Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt   96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20   25   30

96

```
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg    144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc    192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc    240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tat tac tgt    288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95         .

gcg aga gat agc agt ggg ttc tac ggt atg gac gtc tgg ggc caa ggg    336
Ala Arg Asp Ser Ser Gly Phe Tyr Gly Met Asp Val Trp Gly Gln Gly
            100                 105                 110

acc acg gtc acc gtc tca agc                                        357
Thr Thr Val Thr Val Ser Ser
        115
```

```
<210>   142
<211>   119
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   142
```

```
Gln Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Ser Ser Gly Phe Tyr Gly Met Asp Val Trp Gly Gln Gly
```

```
            100                 105                    110
```

Thr Thr Val Thr Val Ser Ser
          115

<210>   143
<211>   360
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region

<220>
<221>   CDS
<222>   (1)..(360)

<400>   143
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg   48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt   96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
              20   25   30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg   144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
          35   40   45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc   192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
      50   55   60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc   240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65   70   75   80

ctg aag ctg agc tct gtg act gcc gcg gac acg gcc gtg tat tac tgt   288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
              85   90   95

gcg aga agc agc agc tgg tac tgg aat gct ttt gat atc tgg ggc caa   336
Ala Arg Ser Ser Ser Trp Tyr Trp Asn Ala Phe Asp Ile Trp Gly Gln
          100   105   110

ggg aca atg gtc acc gtc tca agc   360
Gly Thr Met Val Thr Val Ser Ser
          115   120

<210>   144
<211>   120
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   144

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5               10              15
```

```
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30
```

```
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45
```

```
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60
```

```
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80
```

```
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85              90              95
```

```
Ala Arg Ser Ser Ser Trp Tyr Trp Asn Ala Phe Asp Ile Trp Gly Gln
            100             105             110
```

```
Gly Thr Met Val Thr Val Ser Ser
        115             120
```

<210>   145
<211>   351
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region

<220>
<221>   CDS
<222>   (1)..(351)

<400>   145
```
cag gtg cag cta cag cag tgg ggc cca gca ctg gtg aag cct tcg ggg        48
Gln Val Gln Leu Gln Gln Trp Gly Pro Ala Leu Val Lys Pro Ser Gly
1               5               10              15
```

```
acc ctg tcc ctc acc tgc tct gtc tct ggt gtc tcc atc acc agt aat        96
Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Val Ser Ile Thr Ser Asn
            20              25              30
```

```
atc tgg tgg agt tgg gtc cgc cag tcc cca ggg aag ggg ctg gag tgg       144
Ile Trp Trp Ser Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp
        35              40              45
```

```
att ggg gaa gtc tat cat agt ggg agc acc aac tac aac ccg tcc ctc        192
Ile Gly Glu Val Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc        240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gct gtg tat tac tgt        288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg ggg tac cgt agc ttc ggg gag tcc tac tgg ggc cag gga acc ctg        336
Ala Gly Tyr Arg Ser Phe Gly Glu Ser Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

gtc acc gtc tca agc                                                    351
Val Thr Val Ser Ser
            115
```

```
<210>    146
<211>    117
<212>    PRT
<213>    Artificial

<220>
<223>    Synthetic Construct

<400>    146

Gln Val Gln Leu Gln Gln Trp Gly Pro Ala Leu Val Lys Pro Ser Gly
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Val Ser Ile Thr Ser Asn
            20                  25          -       30

Ile Trp Trp Ser Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Ile Gly Glu Val Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55                  60       .

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Gly Tyr Arg Ser Phe Gly Glu Ser Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
            115
```

```
<210>    147
<211>    366
<212>    DNA
<213>    Artificial

<220>
<223>    heavy chain variable region


<220>
<221>    CDS
<222>    (1)..(366)

<400>    147
cag gtg cag cta cag cag tgg ggc gca ggg ctg ttg aag cct tcg gag      48
Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1               5                   10                  15

acc ctg tct ctc acc tgc gtt gtc tat ggt ggg tcc ttc agc gat ttc      96
Thr Leu Ser Leu Thr Cys Val Val Tyr Gly Gly Ser Phe Ser Asp Phe
                20                  25                  30

tac tgg agc tgg atc cgc cag ccc cca ggg aag ggg cca gag tgg att     144
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Pro Glu Trp Ile
            35                  40                  45

ggg gaa gtc aat cct aga gga agc acc aac tac aac ccg tcc ctc aag     192
Gly Glu Val Asn Pro Arg Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
        50                  55                  60

agt cga gcc acc ata tca cta gac acg tcc aag aac cag ttc tcc ctg     240
Ser Arg Ala Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

aag ctg agt tct gtg acc gcc gcg gac acg gct gtg tat ttc tgt gcg     288
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala
                85                  90                  95

aga ggt cct cgg ccc ggg aga gat ggc tac aat tac ttt gac aac tgg     336
Arg Gly Pro Arg Pro Gly Arg Asp Gly Tyr Asn Tyr Phe Asp Asn Trp
            100                 105                 110

ggc cag ggc acc ctg gtc acc gtc tca agc                             366
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            115                 120


<210>    148
<211>    122
<212>    PRT
<213>    Artificial

<220>
<223>    Synthetic Construct

<400>    148

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1               5                   10                  15
```

Thr Leu Ser Leu Thr Cys Val Val Tyr Gly Gly Ser Phe Ser Asp Phe
              20   25   30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Pro Glu Trp Ile
          35   40   45

Gly Glu Val Asn Pro Arg Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50   55   60

Ser Arg Ala Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe Ser Leu
65   70   75   80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala
              85   90   95

Arg Gly Pro Arg Pro Gly Arg Asp Gly Tyr Asn Tyr Phe Asp Asn Trp
              100   105   110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
          115   120

<210>   149
<211>   357
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region

<220>
<221>   CDS
<222>   (1)..(357)

<400>   149
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag   48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc agc agt agt   96
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
              20   25   30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg   144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
          35   40   45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc   192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50   55   60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc   240

102

```
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80
```

```
ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt      288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85              90              95
```

```
gcg aga ggt ata gca gca gct ggt caa ggt gac tac tgg ggc cag gga      336
Ala Arg Gly Ile Ala Ala Ala Gly Gln Gly Asp Tyr Trp Gly Gln Gly
            100             105             110
```

```
acc ctg gtc acc gtc tca agc                                          357
Thr Leu Val Thr Val Ser Ser
        115
```

```
<210>    150
<211>    119
<212>    PRT
<213>    Artificial

<220>
<223>    Synthetic Construct

<400>    150
```

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5               10              15
```

```
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30
```

```
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45
```

```
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60
```

```
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80
```

```
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85              90              95
```

```
Ala Arg Gly Ile Ala Ala Ala Gly Gln Gly Asp Tyr Trp Gly Gln Gly
            100             105             110
```

```
Thr Leu Val Thr Val Ser Ser
        115
```

```
<210>    151
<211>    363
<212>    DNA
```

<213>   Artificial

<220>
<223>   heavy chain variable region

<220>
<221>   CDS
<222>   (1)..(363)

<400>   151
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag   48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc agc agt agt   96
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
                20   25   30

agt tac tac tgg ggc tgg atc cgc cag ccc cca ggg aag ggg ctg gag   144
Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
            35   40   45

tgg att ggg agt atc tat tat agt ggg agc acc tac tac aac ccg tcc   192
Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
        50   55   60

ctc aag agt cga gtc acc ata tcc gta gac acg tcc aag aac cag ttc   240
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65   70   75   80

tcc ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac   288
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85   90   95

tgt gcg aga gat ggg gga tac tac tac tac ggt atg gac gtc tgg ggc   336
Cys Ala Arg Asp Gly Gly Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly
            100   105   110

caa ggg acc acg gtc acc gtc tca agc   363
Gln Gly Thr Thr Val Thr Val Ser Ser
            115   120

<210>   152
<211>   121
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   152

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
                20   25   30

```
Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
        35                  40                  45


Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
    50                  55                  60


Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80


Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95


Cys Ala Arg Asp Gly Gly Tyr Tyr Tyr Gly Met Asp Val Trp Gly
            100                 105                 110


Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 153
<211> 351
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(351)

<400> 153
```
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg      48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
```

```
                    85                    90                    95
gcg agt agt ggt tat gat gct ttt gat atc tgg ggc caa ggg acc acg        336
Ala Ser Ser Gly Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Thr
            100             105             110

gtc acc gtc tca agc                                                    351
Val Thr Val Ser Ser
        115
```

```
<210>   154
<211>   117
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   154

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5               10              15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85              90              95


Ala Ser Ser Gly Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Thr
            100             105             110


Val Thr Val Ser Ser
        115
```

```
<210>   155
<211>   357
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region
```

```
<220>
<221>   CDS
<222>   (1)..(357)

<400>   155
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg          48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt          96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

aat tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg         144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc         192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc         240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt         288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gca cga tac agc tat gga acg gta gga att gac tac tgg ggc cag gga         336
Ala Arg Tyr Ser Tyr Gly Thr Val Gly Ile Asp Tyr Trp Gly Gln Gly
            100                 105                 110

acc ctg gtc acc gtc tca agc                                             357
Thr Leu Val Thr Val Ser Ser
            115


<210>   156
<211>   119
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   156

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45
```

```
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55                  60
```

```
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70                  75                  80
```

```
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Tyr Ser Tyr Gly Thr Val Gly Ile Asp Tyr Trp Gly Gln Gly
            100                 105                 110
```

```
Thr Leu Val Thr Val Ser Ser
        115
```


<210> 157
<211> 351
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(351)
<223> heavy chain variable region

<400> 157

```
gag gtg cag ctg gtg cag tct ggg gga ggc gtg gtc cag cct ggg acg      48
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Thr
1               5                   10                  15
```

```
tcc ctg aga ctc tcc tgt gca gcc tct gga ttc agc ttc aga agt cat      96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Arg Ser His
            20                  25                  30
```

```
ggc atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg gag tgg gtg     144
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
gca gtt ata tca tat gat gga agt aat aaa tac tat gca gac tcc gtg     192
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60
```

```
aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat     240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
```

```
ctg caa atg aac agc ctg aga gct gag gac acg gct gtg tat tac tgt     288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
gcg act ata ggg ccg ggg gga ttt gac tac tgg ggc cag ggc acc ctg     336
Ala Thr Ile Gly Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu
```

```
            100                 105                 110

gtc acc gtc tca agc                                                   351
Val Thr Val Ser Ser
        115


<210>  158
<211>  117
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  158

Glu Val Gln Leu Val Gln Ser Gly Gly Val Val Gln Pro Gly Thr
1               5               10              15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Arg Ser His
            20              25              30


Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35              40              45


Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50              55              60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70              75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85              90              95


Ala Thr Ile Gly Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100             105             110


Val Thr Val Ser Ser
        115


<210>  159
<211>  357
<212>  DNA
<213>  Artificial

<220>
<223>  heavy chain variable region


<220>
<221>  CDS
<222>  (1)..(357)
```

```
<400>  159
cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg gag      48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15

acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc att aga aat tac      96
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Asn Tyr
            20                  25                  30

tac tgg agt tgg atc cgg cag ccc cca ggg aag gga ctg gag tgg att     144
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

ggg tat att tct gac agt ggg aat acc aac tac aat ccc tcc ctc aag     192
Gly Tyr Ile Ser Asp Ser Gly Asn Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

agt cga gtc acc ata tca gta gac acg tcc aag aac cag ttc tcc cta     240
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

aag ctg acc tct gtg acc gcc aca gac acg gct gcg tat ttc tgt gcg     288
Lys Leu Thr Ser Val Thr Ala Thr Asp Thr Ala Ala Tyr Phe Cys Ala
                85                  90                  95

aga cat cga agc agc tgg gca tgg tac ttc gat ctc tgg ggc cgt ggc     336
Arg His Arg Ser Ser Trp Ala Trp Tyr Phe Asp Leu Trp Gly Arg Gly
            100                 105                 110

acc ctg gtc acc gtc tca agc                                         357
Thr Leu Val Thr Val Ser Ser
            115


<210>  160
<211>  119
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  160

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Arg Asn Tyr
            20                  25                  30


Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Tyr Ile Ser Asp Ser Gly Asn Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60
```

```
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80


Lys Leu Thr Ser Val Thr Ala Thr Asp Thr Ala Ala Tyr Phe Cys Ala
                    85                  90                  95


Arg His Arg Ser Ser Trp Ala Trp Tyr Phe Asp Leu Trp Gly Arg Gly
                100                 105                 110


Thr Leu Val Thr Val Ser Ser
            115
```

```
<210>  161
<211>  354
<212>  DNA
<213>  Artificial

<220>
<223>  heavy chain variable region


<220>
<221>  CDS
<222>  (1)..(354)

<400>  161
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag       48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt       96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20                  25                  30


aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg      144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35                  40                  45


att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc      192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60


aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc      240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt      288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


gcg aga gtg ggc agt ggc tgg tac gtt gac tac tgg ggc cag gga acc      336
Ala Arg Val Gly Ser Gly Trp Tyr Val Asp Tyr Trp Gly Gln Gly Thr
                100                 105                 110


ctg gtc acc gtc tca agc                                              354
Leu Val Thr Val Ser Ser
            115
```

<210> 162
<211> 118
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 162

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20   25   30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35   40   45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65   70   75   80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Val Gly Ser Gly Trp Tyr Val Asp Tyr Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
            115

<210> 163
<211> 360
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(360)

<400> 163
cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg   48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

```
acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt        96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg       144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc       192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc       240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt       288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga gtt tct ggc tac tac tac tac ggt atg gac gtc tgg ggc caa       336
Ala Arg Val Ser Gly Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln
            100                 105                 110

ggg acc acg gtc acc gtc tca agc                                       360
Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 164
<211> 120
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 164

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5               10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
```

```
                85                      90                      95

  Ala Arg Val Ser Gly Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln
              100                 105                 110


  Gly Thr Thr Val Thr Val Ser Ser
          115                 120


  <210>  165
  <211>  369
  <212>  DNA
  <213>  Artificial

  <220>
  <223>  heavy chain variable region


  <220>
  <221>  CDS
  <222>  (1)..(369)


  <400>  165
  gag gtc cag ctg gta cag tct ggg gga ggc gtg gtc cag cct ggg agg     48
  Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
  1               5                   10                  15

  tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttc agt agc tat     96
  Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
              20                  25                  30

  ggc atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg gag tgg gtg    144
  Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35                  40                  45

  gca gtt ata tca tat gat gga agt aat aaa tac tat gca gac tcc gtg    192
  Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
      50                  55                  60

  aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat    240
  Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
  65                  70                  75                  80

  ctg caa atg aac agc ctg aga gct gag gac acg gct gtg tat tac tgt    288
  Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                      85                  90                  95

  gcg aaa gcg tat agc agt ggc tgg tac gac tac tac ggt atg gac gtc    336
  Ala Lys Ala Tyr Ser Ser Gly Trp Tyr Asp Tyr Tyr Gly Met Asp Val
                  100                 105                 110

  tgg ggc caa ggg acc acg gtc acc gtc tca agc                        369
  Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
              115                 120


  <210>  166
  <211>  123
  <212>  PRT
```

<213> Artificial

<220>
<223> Synthetic Construct

<400> 166

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Lys Ala Tyr Ser Ser Gly Trp Tyr Asp Tyr Tyr Gly Met Asp Val
            100   105   110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            115   120

<210> 167
<211> 351
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(351)

<400> 167
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg   48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt   96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20   25   30

```
aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg    144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                      40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc    192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                      55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc    240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                      70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt    288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                      90                  95

gcg aga gcc agc gtt gat gct ttt gat atc tgg ggc caa ggg aca atg    336
Ala Arg Ala Ser Val Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
                100                     105                 110

gtc acc gtc tca agc                                                 351
Val Thr Val Ser Ser
        115
```

```
<210>  168
<211>  117
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  168
```

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                      40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                      55                  60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                      70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                      90                  95


Ala Arg Ala Ser Val Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
                100                     105                 110
```

```
Val Thr Val Ser Ser
        115


<210>   169
<211>   357
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region


<220>
<221>   CDS
<222>   (1)..(357)


<400>   169
cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg    48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5               10              15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt    96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20              25              30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg   144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35              40              45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc   192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc   240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80

ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tac tac tgt   288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85              90              95

gcg aga ggg ctg ggg gat agt agt ggt tat atc ctt tgg ggc caa ggg   336
Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly
            100             105             110

aca atg gtc acc gtc tca agc                                       357
Thr Met Val Thr Val Ser Ser
        115


<210>   170
<211>   119
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct
```

<400> 170

Gln 1	Val	Gln	Leu	Gln 5	Glu	Ser	Gly	Pro	Gly 10	Leu	Val	Lys	Pro	Ser 15	Gly

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
　　　　　　20　　　　　　　　　　25　　　　　　　　30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
　　　　35　　　　　　　　　40　　　　　　　　45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
　　50　　　　　　　　55　　　　　　　60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65　　　　　　　70　　　　　　　75　　　　　　　80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
　　　　　　85　　　　　　　90　　　　　　　95

Ala Arg Gly Leu Gly Asp Ser Ser Gly Tyr Ile Leu Trp Gly Gln Gly
　　　　　100　　　　　　　105　　　　　　　110

Thr Met Val Thr Val Ser Ser
　　　　115

<210> 171
<211> 348
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(348)

<400> 171
```
cag gta cag ctg cag cag tca ggc cca gga ctg gtg aag cct tcg ggg        48
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt       96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg      144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc      192
```

```
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc   240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg act ccc gag gac acg gct gtg tat tac tgt   288
Leu Lys Leu Ser Ser Val Thr Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gca aga gat cac ggc ccc ttt gac tac tgg ggc cgg gga acc ctg gtc   336
Ala Arg Asp His Gly Pro Phe Asp Tyr Trp Gly Arg Gly Thr Leu Val
            100                 105                 110

acc gtc tca agc                                                   348
Thr Val Ser Ser
        115
```

```
<210>  172
<211>  116
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  172
```

```
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                  10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp His Gly Pro Phe Asp Tyr Trp Gly Arg Gly Thr Leu Val
            100                 105                 110


Thr Val Ser Ser
        115
```

<210> 173
<211> 360
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(360)

<400> 173

```
cag gtg cag ctg gtg caa tct ggg gga ggc gtg gtc cag cct ggg agg        48
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

tcc ctg aga ctc tcc tgt gca gcc tct gga ttc gcc ttc agt agc tat        96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ser Tyr
                20                  25                  30

ggc atg cac tgg gtc cgc cag gct cca ggg aag ggg ctg gag tgg gtt       144
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
            35                  40                  45

tca tac att agt agt agt agt agt acc ata tac tac gca gac tct gtg       192
Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
        50                  55                  60

aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat       240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

ctg caa atg aac agc ctg aga gcc gag gac acg gct gtg tat tac tgt       288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga gat cga ttt ggg tcg ggg cac ttg ccc gac tac tgg ggc cag       336
Ala Arg Asp Arg Phe Gly Ser Gly His Leu Pro Asp Tyr Trp Gly Gln
                100                 105                 110

gga acc ctg gtc acc gtc tca agc                                       360
Gly Thr Leu Val Thr Val Ser Ser
            115                 120
```


<210> 174
<211> 120
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 174

```
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15
```

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ser Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Phe Gly Ser Gly His Leu Pro Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

```
<210>   175
<211>   357
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region


<220>
<221>   CDS
<222>   (1)..(357)

<400>   175
cag gtg cag cta cag cag tgg ggc gca gga ctg ttg aag cct tcg gag      48
Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tat ggt ggg tcc ttc agt ggt tac      96
Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
            20                  25                  30

tac tgg agc tgg atc cgc cag ccc cca ggg aag ggg ctg gag tgg att     144
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

ggg gaa atc aat cat agt gga agc acc aac tac aac ccg tcc ctc aag     192
Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

agt cga gtc acc ata tca gta gac acg tcc aag aac cag ttc tcc ctg     240
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
```

65   70   75   80

```
aag ctg agc tct gtg acc gcc gcg gac acg gct gtg tat tac tgt gcg      288
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

aga gtt ggg tat agc agt ggc cgt gac gtt gac tac tgg ggc cag ggc      336
Arg Val Gly Tyr Ser Ser Gly Arg Asp Val Asp Tyr Trp Gly Gln Gly
            100                 105                 110

acc ctg gtc acc gtc tca agc                                          357
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 176
<211> 119
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 176

```
Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
            20                  25                  30


Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80


Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Arg Val Gly Tyr Ser Ser Gly Arg Asp Val Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser
        115
```

<210> 177
<211> 360
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(360)

<400> 177
gag gtc cag ctg gtg gag tct ggc cca gga ctg gtg aag cct tcg ggg   48
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt   96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20   25   30

aac tgg tgg agt tgg atc cgg cag ccc cca ggg aag ggg ctg gag tgg   144
Asn Trp Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35   40   45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc   192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
        50   55   60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc   240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65   70   75   80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt   288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

gcg aga gat agc agc agc tgg tac tac ggt atg gac gtc tgg ggc caa   336
Ala Arg Asp Ser Ser Ser Trp Tyr Tyr Gly Met Asp Val Trp Gly Gln
            100   105   110

ggg acc acg gtc acc gtc tca agc   360
Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 178
<211> 120
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 178

Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20   25   30

```
Asn Trp Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40              45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55                  60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70                  75                  80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85                  90                  95

Ala Arg Asp Ser Ser Ser Trp Tyr Tyr Gly Met Asp Val Trp Gly Gln
            100             105             110

Gly Thr Thr Val Thr Val Ser Ser
        115             120
```

```
<210>   179
<211>   348
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region


<220>
<221>   CDS
<222>   (1)..(348)

<400>   179
gag gtc cag ctg gtg gag tcc ggc cca gga ctg gtg aag cct tcg gag      48
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gta tat tat tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85                  90                  95
```

```
gcg aga tcg acg tgg tcc ctt gac tac tgg ggc cag ggc acc ctg gtc        336
Ala Arg Ser Thr Trp Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100             105             110

acc gtc tca agc                                                        348
Thr Val Ser Ser
        115
```

```
<210>  180
<211>  116
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  180
```

```
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5               10              15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85              90              95


Ala Arg Ser Thr Trp Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100             105             110


Thr Val Ser Ser
        115
```

```
<210>  181
<211>  354
<212>  DNA
<213>  Artificial

<220>
<223>  heavy chain variable region
```

```
<220>
<221>  CDS
<222>  (1)..(354)

<400> 181
gag gtc cag ctg gtg gag tct ggc cca gga ctg gtg aag cct tcg ggg    48
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt    96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg   144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc   192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc   240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gta tat tac tgt   288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga ctc tcg ttt gcc gat cct ttt gat atc tgg ggc caa ggg aca   336
Ala Arg Leu Ser Phe Ala Asp Pro Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110

atg gtc acc gtc tca agc                                           354
Met Val Thr Val Ser Ser
            115


<210>  182
<211>  118
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400> 182

Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
```

```
            50                      55                      60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                   70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                    85                  90                  95


Ala Arg Leu Ser Phe Ala Asp Pro Phe Asp Ile Trp Gly Gln Gly Thr
                100                 105                 110


Met Val Thr Val Ser Ser
          115
```

<210> 183
<211> 366
<212> DNA
<213> Artificial

<220>
<223>   heavy chain variable region

<220>
<221>   CDS
<222>   (1)..(366)

<400>   183
```
cag gtc cag ctg gtg cag tct ggg gct gag gtg aag aag cct ggg tcc       48
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

tcg gtg aag gtc tcc tgc aag gct tct gga ggc acc ttc agc agc tat       96
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
                20                  25                  30

gct atc agc tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg      144
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
            35                  40                  45

gga agg atc atc ccc atc ctt ggt ata gca aac tac gca cag aag ttc      192
Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

cag ggc aga gtc acg att acc gcg gac aaa tcc acg agc aca gcc tac      240
Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

atg gag ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt      288
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gca tat ggt tcg ggg agt tat tac gac tac tac tac atg gac gtc tgg      336
Ala Tyr Gly Ser Gly Ser Tyr Tyr Asp Tyr Tyr Tyr Met Asp Val Trp
            100                 105                 110
```

ggc aaa ggg acc acg gtc acc gtc tca agc   366
Gly Lys Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 184
<211> 122
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 184

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20   25   30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
            35   40   45

Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Tyr Gly Ser Gly Ser Tyr Tyr Asp Tyr Tyr Tyr Met Asp Val Trp
            100   105   110

Gly Lys Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 185
<211> 357
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(357)

<400> 185·

```
gag gtc cag ctg gtg cag tct ggg gga ggc ttg gtc cag cct ggg ggg      48
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

tcc ctg aga ctc tcc tgt tca gcc tcc gga ttc acc ttc agt agc tat      96
Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Ser Tyr
                20                  25                  30

gct atg cac tgg gtc cgc cag gct cca ggg aag gga ctg gaa tat gtt     144
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Tyr Val
            35                  40                  45

tca act att agt agt aat ggg gat agc aca tac tac gca gac tcc gtg     192
Ser Thr Ile Ser Ser Asn Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val
        50                  55                  60

aag ggc aga ttc acc atc tcc aga gac aat tcc aag aac acg ctg tat     240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

ctg caa atg aac agc ctg aga gct gag gac acg gct gtg tat tac tgt     288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aaa gaa gaa gta tgg cta cag gct ttt gat atc tgg ggc caa ggg     336
Ala Lys Glu Glu Val Trp Leu Gln Ala Phe Asp Ile Trp Gly Gln Gly
                100                 105                 110

aca atg gtc acc gtc tca agc                                          357
Thr Met Val Thr Val Ser Ser
            115
```

```
<210>   186
<211>   119
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   186
```

```
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Ser Tyr
                20                  25                  30


Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Tyr Val
            35                  40                  45


Ser Thr Ile Ser Ser Asn Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val
        50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
```

```
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Lys Glu Glu Val Trp Leu Gln Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110


Thr Met Val Thr Val Ser Ser
        115
```

```
<210>  187
<211>  345
<212>  DNA
<213>  Artificial

<220>
<223>  heavy chain variable region


<220>
<221>  CDS
<222>  (1)..(345)


<400>  187
cag ctg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag    48
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1                   5                   10                  15


acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc agt agt aac    96
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Asn
            20                  25                  30


tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg att   144
Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


ggg gaa atc tat cat agt ggg agc acc aac tac aac ccc tcc ctc aag   192
Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


agt cga gtc acc atc tca gta gac acg tcc aag aac cag ttc tcc ctg   240
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80


aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tat tac tgt gcg   288
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
            85                  90                  95


aga gat aag gga tac atg gac gtc tgg ggc aaa ggg acc acg gtc acc   336
Arg Asp Lys Gly Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr
            100                 105                 110


gtc tca agc                                                        345
Val Ser Ser
        115
```

130

```
<210>    188
<211>    115
<212>    PRT
<213>    Artificial

<220>
<223>    Synthetic Construct

<400>    188
```

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Asn
            20   25   30

Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50   55   60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65   70   75   80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Arg Asp Lys Gly Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr
            100   105   110

Val Ser Ser
        115

```
<210>    189
<211>    363
<212>    DNA
<213>    Artificial

<220>
<223>    heavy chain variable region

<220>
<221>    CDS
<222>    (1)..(363)

<400>    189
```

cag gta cag ctg cag cag tca ggg gct gag gtg aag aag cct ggg tcc   48
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1   5   10   15

tcg gtg aag gtc tcc tgc aag gct tct gga ggc acc ttc agc agc tat   96

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30

gct atc agc tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg      144
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
            35                  40                  45

gga agg atc atc cct atc ctt ggt ata gca aac tac gca cag aag ttc      192
Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
        50                  55                  60

cag ggc aga gtc acg att acc gcg gac aaa tcc acg agc aca gcc tac      240
Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

atg gag ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt      288
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                    85                  90                  95

gcg aga gat cat agg ttc gac tac gcc tgg tac ttc gat ctc tgg ggc      336
Ala Arg Asp His Arg Phe Asp Tyr Ala Trp Tyr Phe Asp Leu Trp Gly
            100                 105                 110

cgt ggc acc ctg gtc acc gtc tca agc                                  363
Arg Gly Thr Leu Val Thr Val Ser Ser
            115                 120
```

```
<210>    190
<211>    121
<212>    PRT
<213>    Artificial

<220>
<223>    Synthetic Construct

<400>    190
```

```
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30


Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
            35                  40                  45


Gly Arg Ile Ile Pro Ile Leu Gly Ile Ala Asn Tyr Ala Gln Lys Phe
        50                  55                  60


Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                    85                  90                  95
```

```
Ala Arg Asp His Arg Phe Asp Tyr Ala Trp Tyr Phe Asp Leu Trp Gly
            100                 105             110


Arg Gly Thr Leu Val Thr Val Ser Ser
            115                 120
```

<210> 191
<211> 351
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS
<222> (1)..(351)

<400> 191
```
cag gtg cag ctg cag gag tcg ggc cca gga ctg ctg aag cct tcg ggg      48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Leu Lys Pro Ser Gly
1                   5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agc      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg gag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtc tat tac tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga gat cta acg ggg agt ctt gac tac tgg ggc cag gga acc ctg     336
Ala Arg Asp Leu Thr Gly Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu
                100                 105                 110

gtc acc gtc tca agc                                                 351
Val Thr Val Ser Ser
            115
```

<210> 192
<211> 117
<212> PRT
<213> Artificial

<220>
<223>   Synthetic Construct

<400>   192

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Leu Lys Pro Ser Gly
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20   25   30

Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Glu Gly Leu Glu Trp
        35   40   45

Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50   55   60

Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65   70   75   80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85   90   95

Ala Arg Asp Leu Thr Gly Ser Leu Asp Tyr Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser
            115

<210>   193
<211>   351
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region

<220>
<221>   CDS
<222>   (1)..(351)

<400>   193
cag gtg cag ctg cag gag tcc ggc cca gga ctg gtg aag cct tcg ggg   48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1   5   10   15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt   96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20   25   30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg   144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp

134

```
               35                    40                    45
att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc      192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc      240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt      288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga ata cgc tat gat gct ttt gat atc tgg ggc caa ggg aca atg      336
Ala Arg Ile Arg Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
            100                 105                 110

gtc acc gtc tca agc                                                  351
Val Thr Val Ser Ser
        115
```

<210> 194
<211> 117
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 194

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Ile Arg Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
            100                 105                 110
```

```
Val Thr Val Ser Ser
        115


<210>   195
<211>   354
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region


<220>
<221>   CDS
<222>   (1)..(354)

<400>   195
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag      48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
                20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
            35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
        50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tat tac tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcc gtg acg gca gcc cat gat gct ttt gat atc tgg ggc caa ggg aca     336
Ala Val Thr Ala Ala His Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
                100                 105                 110

atg gtc acc gtc tca agc                                             354
Met Val Thr Val Ser Ser
        115


<210>   196
<211>   118
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   196
```

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5               10              15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75              80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
            85              90              95


Ala Val Thr Ala Ala His Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100             105             110


Met Val Thr Val Ser Ser
        115
```

```
<210>  197
<211>  357
<212>  DNA
<213>  Artificial

<220>
<223>  heavy chain variable region


<220>
<221>  CDS
<222>  (1)..(357)


<400>  197
cag gtg cag cta cag cag tgg ggc cca gga ctg gtg aag cct tcg ggg       48
Gln Val Gln Leu Gln Gln Trp Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5               10              15


acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt       96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30


aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg      144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45


att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc      192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60
```

137

```
aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc      240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75                      80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt      288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85              90                      95

gcg aga gac agc agt ggc caa ggg tac ttt gac tac tgg ggc cag ggc      336
Ala Arg Asp Ser Ser Gly Gln Gly Tyr Phe Asp Tyr Trp Gly Gln Gly
            100             105             110

acc ctg gtc acc gtc tca agc                                          357
Thr Leu Val Thr Val Ser Ser
        115
```

```
<210>   198
<211>   119
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   198
```

```
Gln Val Gln Leu Gln Gln Trp Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5               10              15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20              25              30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35              40              45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50              55              60


Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65              70              75                      80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85              90                      95


Ala Arg Asp Ser Ser Gly Gln Gly Tyr Phe Asp Tyr Trp Gly Gln Gly
            100             105             110


Thr Leu Val Thr Val Ser Ser
        115
```

```
<210>   199
```

```
<211>   354
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region


<220>
<221>   CDS
<222>   (1)..(354)

<400>   199
gag gtg cag ctg gtg cag tct ggg gct gag gtg aag aag cct ggg gcc      48
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

tca gtg aag gtc tcc tgc aag gct tct gga tac acc ttc act agc tat      96
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

gct atg cat tgg gtg cgc cag gcc ccc gga caa agg ctt gag tgg atg     144
Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

gga tgg atc aac gct ggc aat ggt aac aca aaa tat tca cag aag ttc     192
Gly Trp Ile Asn Ala Gly Asn Gly Asn Thr Lys Tyr Ser Gln Lys Phe
    50                  55                  60

cag ggc aga gtc acc atg acc agg gac acg tcc acg agc aca gtc tac     240
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

atg gag ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt     288
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gct aga cac tcg tac tac tac ggt atg gac gtc tgg ggc caa ggc acc     336
Ala Arg His Ser Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
            100                 105                 110

ctg gtc acc gtc tca agc                                             354
Leu Val Thr Val Ser Ser
        115


<210>   200
<211>   118
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   200

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
```

```
                20                      25                      30
```

```
Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45
```

```
Gly Trp Ile Asn Ala Gly Asn Gly Asn Thr Lys Tyr Ser Gln Lys Phe
    50                  55                  60
```

```
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80
```

```
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg His Ser Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
            100                 105                 110
```

```
Leu Val Thr Val Ser Ser
            115
```

```
<210>   201
<211>   360
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region


<220>
<221>   CDS
<222>   (1)..(360)

<400>   201
cag gtg cag cta cag cag tgg ggc gca gga ctg ttg aag cct tcg gag    48
Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tat ggt ggg tcc ttc agt ggt tac    96
Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
                20                  25                  30

tac tgg agc tgg atc cgc cag ccc cca ggg aag ggg ctg gag tgg att   144
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
            35                  40                  45

ggg gaa atc aat cat agt gga agc acc aac tac aac ccg tcc ctc aag   192
Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
        50                  55                  60

agt cga gtc acc ata tcg gta gac acg tcc aag aac cag ttc tcc ctg   240
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80
```

```
aag ctg agc tct gtg acc gcc gcg gac acg gct gtg tat tac tgt gcg       288
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                    85                  90                  95

aga gtc ggg tat agc cac ggc gaa gaa gtc ctg gac gtc tgg ggc aaa       336
Arg Val Gly Tyr Ser His Gly Glu Glu Val Leu Asp Val Trp Gly Lys
                100                 105                 110

ggg acc acg gtc acc gtc tca agc                                       360
Gly Thr Thr Val Thr Val Ser Ser
            115                 120
```

```
<210>    202
<211>    120
<212>    PRT
<213>    Artificial

<220>
<223>    Synthetic Construct

<400>    202
```

```
Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1                5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
                20                  25                  30


Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
            35                  40                  45


Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80


Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Arg Val Gly Tyr Ser His Gly Glu Glu Val Leu Asp Val Trp Gly Lys
                100                 105                 110


Gly Thr Thr Val Thr Val Ser Ser
            115                 120
```

```
<210>    203
<211>    354
<212>    DNA
<213>    Artificial

<220>
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<223>   heavy chain variable region

<220>
<221>   CDS
<222>   (1)..(354)

<400>   203
cag gtg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag   48
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc ggc aat tat   96
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Gly Asn Tyr
            20   25   30

gac tgg agt tgg atc cgg cag ccc cca ggg aag gga ctg gag tgg att   144
Asp Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

ggg act atc tac tct agt ggg agt acg tac tac agt ccg tcc ctc aag   192
Gly Thr Ile Tyr Ser Ser Gly Ser Thr Tyr Tyr Ser Pro Ser Leu Lys
        50   55   60

agt cga ctc acc ata tca gta gac aag tcc aag aac cgg ttc tcc ctg   240
Ser Arg Leu Thr Ile Ser Val Asp Lys Ser Lys Asn Arg Phe Ser Leu
65   70   75   80

aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt gcg   288
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

aga gca cga ggg tat agc agc ccc ttc gac ccc tgg ggc cag ggc acc   336
Arg Ala Arg Gly Tyr Ser Ser Pro Phe Asp Pro Trp Gly Gln Gly Thr
                100   105   110

ctg gtc acc gtc tca agc   354
Leu Val Thr Val Ser Ser
            115

<210>   204
<211>   118
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   204

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Gly Asn Tyr
            20   25   30

Asp Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

```
Gly Thr Ile Tyr Ser Ser Gly Ser Thr Tyr Tyr Ser Pro Ser Leu Lys
    50              55                  60
```

```
Ser Arg Leu Thr Ile Ser Val Asp Lys Ser Lys Asn Arg Phe Ser Leu
65              70                  75                  80
```

```
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
            85                  90                  95
```

```
Arg Ala Arg Gly Tyr Ser Ser Pro Phe Asp Pro Trp Gly Gln Gly Thr
            100                 105                 110
```

```
Leu Val Thr Val Ser Ser
        115
```

```
<210>   205
<211>   357
<212>   DNA
<213>   Artificial

<220>
<223>   heavy chain variable region


<220>
<221>   CDS
<222>   (1)..(357)

<400>   205
cag gtc cag ctg gta cag tct ggg gct gag gtg aag aag cct ggg tcc        48
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

tcg gtg aag gtc tcc tgc aag gct tct gga ggc acc ttc agc agc tat        96
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30

gct atc agc tgg gtg cga cag gcc cct gga caa ggg ctt gag tgg atg       144
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

gga ata atc aac cct agt ggt ggt agc aca agc tac gca cag aag ttc       192
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

cag ggc aga gtc acc att acc agg gac aca tcc gcg agc aca gcc tac       240
Gln Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80

atg gag ctg agc agc ctg aga tct gaa gac acg gct gtg tat tac tgt       288
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga gat cgg tgg agg tac gat gct ttt gat atc tgg ggc caa ggg       336
```

```
Ala Arg Asp Arg Trp Arg Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100             105             110

aca atg gtc acc gtc tca agc                                       357
Thr Met Val Thr Val Ser Ser
        115
```

<210> 206
<211> 119
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 206

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5               10              15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20              25              30


Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
            35              40              45


Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50              55              60


Gln Gly Arg Val Thr Ile Thr Arg Asp Thr Ser Ala Ser Thr Ala Tyr
65              70              75              80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85              90              95


Ala Arg Asp Arg Trp Arg Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100             105             110


Thr Met Val Thr Val Ser Ser
        115
```

<210> 207
<211> 348
<212> DNA
<213> Artificial

<220>
<223> heavy chain variable region

<220>
<221> CDS

```
<222>   (1)..(348)

<400>   207
gag gtg cag ctg gtg gag tct ggc cca gga ctg gtg aag cct tcg ggg      48
Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15

acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc agc agt agt      96
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

aac tgg tgg agt tgg gtc cgc cag ccc cca ggg aag ggg ctg gag tgg     144
Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

att ggg gaa atc tat cat agt ggg agc acc aac tac aac ccg tcc ctc     192
Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

aag agt cga gtc acc ata tca gta gac aag tcc aag aac cag ttc tcc     240
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

ctg aag ctg agc tct gtg acc gcc gcg gac acg gcc gtg tat tac tgt     288
Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg aga gaa aaa tcg ggt atg gac gtc tgg ggc caa ggg acc acg gtc     336
Ala Arg Glu Lys Ser Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
            100                 105                 110

acc gtc tca agc                                                      348
Thr Val Ser Ser
        115


<210>   208
<211>   116
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   208


Glu Val Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Asn Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45


Ile Gly Glu Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60
```

```
Lys Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser
65                  70              75                  80


Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85              90                  95


Ala Arg Glu Lys Ser Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
            100             105             110


Thr Val Ser Ser
        115
```

```
<210>   209
<211>   321
<212>   DNA
<213>   Artificial

<220>
<223>   light chain constant region


<220>
<221>   CDS
<222>   (1)..(321)


<400>   209
cga act gtg gct gca cca tct gtc ttc atc ttc ccg cca tct gat gag        48
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15

cag ttg aaa tct gga act gcc tct gtt gtg tgc ctg ctg aat aac ttc        96
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

tat ccc aga gag gcc aaa gta cag tgg aag gtg gat aac gcc ctc caa       144
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
            35                  40                  45

tcg ggt aac tcc cag gag agt gtc aca gag cag gac agc aag gac agc       192
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
        50                  55                  60

acc tac agc ctc agc agc acc ctg acg ctg agc aaa gca gac tac gag       240
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

aaa cac aaa gtc tac gcc tgc gaa gtc acc cat cag ggc ctg agc tcg       288
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

ccc gtc aca aag agc ttc aac agg gga gag tgt                           321
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100             105


<210>   210
```

146

<211> 107
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 210

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1   5   10   15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20   25   30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35   40   45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50   55   60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65   70   75   80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
            85   90   95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100   105

<210> 211
<211> 990
<212> DNA
<213> Artificial

<220>
<223> heavy chain constant region

<220>
<221> CDS
<222> (1)..(990)

<400> 211
gcc tcc acc aag ggc cca tcg gtc ttc ccc ctg gca ccc tcc tcc aag   48
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1   5   10   15

agc acc tct ggg ggc aca gcg gcc ctg ggc tgc ctg gtc aag gac tac   96
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20   25   30

ttc ccc gaa ccg gtg acg gtg tcg tgg aac tca ggc gcc ctg acc agc   144
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser

147

```
            35                        40                        45

ggc gtg cac acc ttc ccg gct gtc cta cag tcc tca gga ctc tac tcc    192
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                      55                  60

ctc agc agc gtg gtg acc gtg ccc tcc agc agc ttg ggc acc cag acc    240
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                      70                  75                  80

tac atc tgc aac gtg aat cac aag ccc agc aac acc aag gtg gac aag    288
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

aaa gtt gag ccc aaa tct tgt gac aaa act cac aca tgc cca ccg tgc    336
Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
                100                 105                 110

cca gca cct gaa ctc ctg ggg gga ccg tca gtc ttc ctc ttc ccc cca    384
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
            115                 120                 125

aaa ccc aag gac acc ctc atg atc tcc cgg acc cct gag gtc aca tgc    432
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc aac tgg    480
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

tac gtg gac ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg gag    528
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc ctg    576
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc tcc aac    624
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
            195                 200                 205

aaa gcc ctc cca gcc ccc atc gag aaa acc atc tcc aaa gcc aaa ggg    672
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg gat gag    720
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

ctg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc tat    768
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

ccc agc gac atc gcc gtg gag tgg gag agc aat ggg cag ccg gag aac    816
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc ttc ttc    864
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
            275                 280                 285
```

```
ctc tat agc aag ctc acc gtg gac aag agc agg tgg cag cag ggg aac      912
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290             295             300

gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac tac acg      960
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305             310             315             320

cag aag agc ctc tcc ctg tct ccg ggt aaa                              990
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            325             330
```

```
<210>   212
<211>   330
<212>   PRT
<213>   Artificial

<220>
<223>   Synthetic Construct

<400>   212
```

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5               10              15


Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20              25              30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35              40              45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50              55              60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65              70              75              80


Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
            85              90              95


Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100             105             110


Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115             120             125


Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130             135             140


Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
```

145   150   155   160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
            165   170   175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180   185   190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
            195   200   205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210   215   220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225   230   235   240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
            245   250   255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260   265   270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
            275   280   285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290   295   300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305   310   315   320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            325   330

<210> 213
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Light chain CDR3

<220>
<221> misc_feature
<222> (8)..(8)
<223> Xaa can be any naturally occurring amino acid

```
<400>  213

Met Gln Ala Leu Gln Thr Pro Xaa Thr
1               5


<210>  214
<211>  9
<212>  PRT
<213>  Artificial

<220>
<223>  Light chain CDR3


<220>
<221>  MISC_FEATURE
<222>  (3)..(3)
<223>  x is arginine or serine

<220>
<221>  MISC_FEATURE
<222>  (4)..(4)
<223>  x is asparagine or serine

<220>
<221>  MISC_FEATURE
<222>  (5)..(5)
<223>  x is serine or asparagine

<220>
<221>  MISC_FEATURE
<222>  (6)..(6)
<223>  x is glycine, alanine, valine, leucine, isoleucine, proline,
       phenylalinine, methionine, tryptophan or cysteine

<400>  214

Gln Gln Xaa Xaa Xaa Xaa Pro Leu Thr
1               5


<210>  215
<211>  10
<212>  PRT
<213>  Artificial

<220>
<223>  Light chain CDR3


<220>
<221>  MISC_FEATURE
<222>  (8)..(9)
<223>  x is arginine, valine, or isoleucine or no amino acid

<400>  215

Gln Ser Tyr Asp Ser Ser Asn Xaa Xaa Val
1               5                   10
```

```
<210>  216
<211>  8
<212>  PRT
<213>  Artificial

<220>
<223>  Heavy chain CDR3


<220>
<221>  MISC_FEATURE
<222>  (1)..(8)

<400>  216

Ser Arg Leu Asp Ala Phe Asp Ile
1                   5


<210>  217
<211>  10
<212>  PRT
<213>  Artificial

<220>
<223>  Heavy chain CDR3


<220>
<221>  misc_feature
<222>  (2)..(2)
<223>  Xaa can be any naturally occurring amino acid

<400>  217

Ser Xaa Tyr Asp Tyr Tyr Gly Met Asp Val
1                   5                   10


<210>  218
<211>  11
<212>  PRT
<213>  Artificial

<220>
<223>  Heavy chain CDR3


<220>
<221>  misc_feature
<222>  (3)..(3)
<223>  Xaa can be any naturally occurring amino acid

<220>
<221>  misc_feature
<222>  (5)..(5)
<223>  Xaa can be any naturally occurring amino acid

<400>  218
```

```
His Arg Xaa Asp Xaa Ala Trp Tyr Phe Asp Leu
1               5                   10
```

```
<210>   219
<211>   4
<212>   PRT
<213>   Artificial

<220>
<223>   Heavy chain CDR3


<220>
<221>   MISC_FEATURE
<222>   (1)..(4)

<400>   219
```

```
Asp Ser Ser Gly
1
```

```
<210>   220
<211>   16
<212>   PRT
<213>   Artificial

<220>
<223>   Light chain CDR1


<220>
<221>   MISC_FEATURE
<222>   (1)..(16)

<400>   220
```

```
Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp
1               5                   10                  15
```

```
<210>   221
<211>   11
<212>   PRT
<213>   Artificial

<220>
<223>   Light chain CDR1


<220>
<221>   MISC_FEATURE
<222>   (5)..(5)
<223>   x is glycine or serine

<220>
<221>   MISC_FEATURE
<222>   (6)..(6)
<223>   x is isoleucine or valine
```

```
<220>
<221>  MISC_FEATURE
<222>  (7)..(7)
<223>  x is glycine or serine

<220>
<221>  MISC_FEATURE
<222>  (8)..(8)
<223>  x is any amino acid

<220>
<221>  MISC_FEATURE
<222>  (9)..(9)
<223>  x is tyrosine or phenyalanine

<220>
<221>  MISC_FEATURE
<222>  (11)..(11)
<223>  x is alanine or asparagine

<400>  221

Arg Ala Ser Gln Xaa Xaa Xaa Xaa Xaa Leu Xaa
1               5                   10


<210>  222
<211>  11
<212>  PRT
<213>  Artificial

<220>
<223>  Light chain CDR1


<220>
<221>  MISC_FEATURE
<222>  (6)..(6)
<223>  Xaa is leucine or serine

<220>
<221>  MISC_FEATURE
<222>  (7)..(11)
<223>  x is independently any amino acid

<400>  222

Arg Ser Ser Gln Ser Xaa Xaa Xaa Xaa Xaa Xaa
1               5                   10


<210>  223
<211>  7
<212>  PRT
<213>  Artificial

<220>
<223>  Light chain CDR2

<400>  223
```

154

```
Leu Gly Ser Asn Arg Ala Ser
1               5


<210> 224
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Light chain CDR2

<400> 224

Ala Ala Ser Thr Leu Gln Ser
1               5


<210> 225
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Light chain CDR2


<220>
<221> misc_feature
<222> (4)..(4)
<223> Xaa can be any naturally occurring amino acid

<400> 225

Glu Asp Asn Xaa Arg Pro Ser
1               5


<210> 226
<211> 6
<212> PRT
<213> Artificial

<220>
<223> Heavy chain CDR1

<400> 226

Ser Ser Asn Trp Trp Ser
1               5


<210> 227
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Heavy chain CDR1
```

```
<220>
<221>  misc_feature
<222>  (1)..(1)
<223>  Xaa can be any naturally occurring amino acid


<400>  227


Xaa Tyr Tyr Trp Ser
1                   5



<210>  228
<211>  5
<212>  PRT
<213>  Artificial

<220>
<223>  Heavy chain CDR1


<220>
<221>  MISC_FEATURE
<222>  (5)..(5)
<223>  x is serine or histidine


<400>  228


Ser Tyr Ala Met Xaa
1                   5



<210>  229
<211>  16
<212>  PRT
<213>  Artificial

<220>
<223>  Heavy chain CDR2


<220>
<221>  MISC_FEATURE
<222>  (1)..(1)
<223>  Xaa = glutamic acid or isoleucine

<220>
<221>  MISC_FEATURE
<222>  (2)..(2)
<223>  Xaa = isoleucine or valine

<220>
<221>  MISC_FEATURE
<222>  (3)..(3)
<223>  Xaa = tyrosine or asparagine

<220>
<221>  MISC_FEATURE
<222>  (4)..(4)
<223>  Xaa = histidine or tyrosine

<220>
```

```
<221>  MISC_FEATURE
<222>  (9)..(9)
<223>  Xaa = asparagine or tyrosine


<400>  229

Xaa Xaa Xaa Xaa Ser Gly Ser Thr Xaa Tyr Asn Pro Ser Leu Lys Ser
1               5                   10                  15



<210>  230
<211>  17
<212>  PRT
<213>  Artificial

<220>
<223>  Heavy chain CDR2


<220>
<221>  MISC_FEATURE
<222>  (1)..(1)
<223>  Xaa = any  amino acid

<220>
<221>  MISC_FEATURE
<222>  (4)..(4)
<223>  Xaa = glycine or serine

<220>
<221>  MISC_FEATURE
<222>  (7)..(7)
<223>  Xaa = glycine or serine


<400>  230

Xaa Ile Ser Xaa Ser Gly Xaa Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1               5                   10                  15


Gly



<210>  231
<211>  1162
<212>  PRT
<213>  Artificial

<220>
<223>  huIGF-1R:Fc


<220>
<221>  MISC_FEATURE
<222>  (1)..(1162)


<400>  231

Met Lys Ser Gly Ser Gly Gly Gly Ser Pro Thr Ser Leu Trp Gly Leu
1               5                   10                  15
```

```
Leu Phe Leu Ser Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile
        20              25                  30

Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg
        35              40                  45

Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile
    50              55                  60

Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val
65              70                  75                      80

Ile Thr Glu Tyr Leu Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu
            85                  90                  95

Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe
            100             105                 110

Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile
        115                 120                 125

Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu
    130                 135                 140

Lys Asn Ala Asp Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser Leu Ile
145                 150                 155                 160

Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys
            165                 170                 175

Glu Cys Gly Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys
            180                 185                 190

Glu Lys Thr Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr
        195                 200                 205

Asn Arg Cys Gln Lys Met Cys Pro Ser Thr Cys Gly Lys Arg Ala Cys
        210                 215                 220

Thr Glu Asn Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser
225                 230                 235                 240

Ala Pro Asp Asn Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Tyr
            245                 250                 255
```

```
Ala Gly Val Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu
            260             265                 270

Gly Trp Arg Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala
        275             280                 285

Glu Ser Ser Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met
    290             295                 300

Gln Glu Cys Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr
305             310                 315                 320

Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Glu Lys
            325             330                 335

Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly
            340             345                 350

Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn
        355             360                 365

Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val
    370             375                 380

Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser
385             390                 395                 400

Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly
            405             410                 415

Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp
        420             425                 430

Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe
        435             440                 445

Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu
    450             455                 460

Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg
465             470                 475                 480

Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr
            485             490                 495
```

159

```
Ser Thr Thr Thr Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr
        500             505             510

Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys
        515             520             525

Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys
    530             535             540

Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys
545             550             555             560

Asp Val Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln
            565             570             575

Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp
            580             585             590

His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala
        595             600             605

Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser
    610             615             620

Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn
625             630             635             640

Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr
            645             650             655

Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys
            660             665             670

Tyr Ala Asp Gly Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys
        675             680             685

Thr Glu Val Cys Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys
    690             695             700

Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr Arg Lys
705             710             715             720

Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu
            725             730             735

Arg Lys Arg Arg Asp Val Met Gln Val Ala Asn Thr Thr Met Ser Ser
```

```
                740                    745                    750


   Arg Ser Arg Asn Thr Thr Ala Ala Asp Thr Tyr Asn Ile Thr Asp Pro
           755                 760                 765


   Glu Glu Leu Glu Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp Asn
       770                 775               .   780


   Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr Arg
   785                 790                 795                 800


   Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser
       .           805                 810                 815


   Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala Asp
               820                 825                 830


   Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser Ile
               835                 840                 845


   Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu Met
       850                 855                 860


   Tyr Glu Ile Lys Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu Cys Val
   865                 870                 875                 880


   Ser Arg Gln Glu Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn Arg Leu
               885                 890                 895


   Asn Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser Gly
               900                 905                 910


   Asn Gly Ser Trp Thr Asp Pro Val Phe Phe Tyr Val Gln Ala Lys Thr
           915                 920                 925


   Gly Tyr Glu Asn Phe Ile His Leu Asp Glu Val Asp Gly Cys Lys Pro .
       930                 935                 940


   Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro
   945           .       950                 955                 960


   Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys
               965                 970                 975


   Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp
               980                 985                 990
```

```
Phe Val Asp Asp Val Glu Val His  Thr Ala Gln Thr Gln  Pro Arg Glu
    995                 1000                1005


Glu Gln  Phe Asn Ser Thr Phe  Arg Ser Val Ser Glu  Leu Pro Ile
    1010            1015                1020


Met His  Gln Asp Trp Leu Asn  Gly Lys Glu Phe Lys  Cys Arg Val
    1025            1030                1035


Asn Ser  Ala Ala Phe Pro Ala  Pro Ile Glu Lys Thr  Ile Ser Lys
    1040            1045                1050


Thr Lys  Gly Arg Pro Lys Ala  Pro Gln Val Tyr Thr  Ile Pro Pro
    1055            1060                1065


Pro Lys  Glu Gln Met Ala Lys  Asp Lys Val Ser Leu  Thr Cys Met
    1070            1075                1080


Ile Thr  Asp Phe Phe Pro Glu  Asp Ile Thr Val Glu  Trp Gln Trp
    1085            1090                1095


Asn Gly  Gln Pro Ala Glu Asn  Tyr Lys Asn Thr Gln  Pro Ile Met
    1100            1105                1110


Asp Thr  Asp Gly Ser Tyr Phe  Val Tyr Ser Lys Leu  Asn Val Gln
    1115            1120                1125


Lys Ser  Asn Trp Glu Ala Gly  Asn Thr Phe Thr Cys  Ser Val Leu
    1130            1135                1140


His Glu  Gly Leu His Asn His  His Thr Glu Lys Ser  Leu Ser His
    1145            1150                1155


Ser Pro  Gly Lys
    1160


<210>   232
<211>   1180
<212>   PRT
<213>   Artificial

<220>
<223>   hu INSR:fC


<220>
<221>   MISC_FEATURE
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<222> (1)..(1180)

<400> 232

Met Gly Thr Gly Gly Arg Arg Gly Ala Ala Ala Ala Pro Leu Leu Val
1   5   10   15

Ala Val Ala Ala Leu Leu Leu Gly Ala Ala Gly His Leu Tyr Pro Gly
            20   25   30

Glu Val Cys Pro Gly Met Asp Ile Arg Asn Asn Leu Thr Arg Leu His
        35   40   45

Glu Leu Glu Asn Cys Ser Val Ile Glu Gly His Leu Gln Ile Leu Leu
    50   55   60

Met Phe Lys Thr Arg Pro Glu Asp Phe Arg Asp Leu Ser Phe Pro Lys
65   70   75   80

Leu Ile Met Ile Thr Asp Tyr Leu Leu Leu Phe Arg Val Tyr Gly Leu
            85   90   95

Glu Ser Leu Lys Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Ser
        100   105   110

Arg Leu Phe Phe Asn Tyr Ala Leu Val Ile Phe Glu Met Val His Leu
        115   120   125

Lys Glu Leu Gly Leu Tyr Asn Leu Met Asn Ile Thr Arg Gly Ser Val
    130   135   140

Arg Ile Glu Lys Asn Asn Glu Leu Cys Tyr Leu Ala Thr Ile Asp Trp
145   150   155   160

Ser Arg Ile Leu Asp Ser Val Glu Asp Asn His Ile Val Leu Asn Lys
            165   170   175

Asp Asp Asn Glu Glu Cys Gly Asp Ile Cys Pro Gly Thr Ala Lys Gly
            180   185   190

Lys Thr Asn Cys Pro Ala Thr Val Ile Asn Gly Gln Phe Val Glu Arg
        195   200   205

Cys Trp Thr His Ser His Cys Gln Lys Val Cys Pro Thr Ile Cys Lys
    210   215   220

Ser His Gly Cys Thr Ala Glu Gly Leu Cys Cys His Ser Glu Cys Leu

225   230   235   240

Gly Asn Cys Ser Gln Pro Asp Asp Pro Thr Lys Cys Val Ala Cys Arg
            245   250   255

Asn Phe Tyr Leu Asp Gly Arg Cys Val Glu Thr Cys Pro Pro Pro Tyr
            260   265   270

Tyr His Phe Gln Asp Trp Arg Cys Val Asn Phe Ser Phe Cys Gln Asp
        275   280   285

Leu His His Lys Cys Lys Asn Ser Arg Arg Gln Gly Cys His Gln Tyr
    290   295   300

Val Ile His Asn Asn Lys Cys Ile Pro Glu Cys Pro Ser Gly Tyr Thr
305   310   315   320

Met Asn Ser Ser Asn Leu Leu Cys Thr Pro Cys Leu Gly Pro Cys Pro
            325   330   335

Lys Val Cys His Leu Leu Glu Gly Glu Lys Thr Ile Asp Ser Val Thr
        340   345   350

Ser Ala Gln Glu Leu Arg Gly Cys Thr Val Ile Asn Gly Ser Leu Ile
        355   360   365

Ile Asn Ile Arg Gly Gly Asn Asn Leu Ala Ala Glu Leu Glu Ala Asn
    370   375   380

Leu Gly Leu Ile Glu Glu Ile Ser Gly Tyr Leu Lys Ile Arg Arg Ser
385   390   395   400

Tyr Ala Leu Val Ser Leu Ser Phe Phe Arg Lys Leu Arg Leu Ile Arg
            405   410   415

Gly Glu Thr Leu Glu Ile Gly Asn Tyr Ser Phe Tyr Ala Leu Asp Asn
            420   425   430

Gln Asn Leu Arg Gln Leu Trp Asp Trp Ser Lys His Asn Leu Thr Thr
        435   440   445

Thr Gln Gly Lys Leu Phe Phe His Tyr Asn Pro Lys Leu Cys Leu Ser
    450   455   460

Glu Ile His Lys Met Glu Glu Val Ser Gly Thr Lys Gly Arg Gln Glu
465   470   475   480

Arg Asn Asp Ile Ala Leu Lys Thr Asn Gly Asp Lys Ala Ser Cys Glu
                485   490   495

Asn Glu Leu Leu Lys Phe Ser Tyr Ile Arg Thr Ser Phe Asp Lys Ile
                500   505   510

Leu Leu Arg Trp Glu Pro Tyr Trp Pro Pro Asp Phe Arg Asp Leu Leu
                515   520   525

Gly Phe Met Leu Phe Tyr Lys Glu Ala Pro Tyr Gln Asn Val Thr Glu
    530   535   540

Phe Asp Gly Gln Asp Ala Cys Gly Ser Asn Ser Trp Thr Val Val Asp
545   550   555   560

Ile Asp Pro Pro Leu Arg Ser Asn Asp Pro Lys Ser Gln Asn His Pro
                565   570   575

Gly Trp Leu Met Arg Gly Leu Lys Pro Trp Thr Gln Tyr Ala Ile Phe
                580   585   590

Val Lys Thr Leu Val Thr Phe Ser Asp Glu Arg Arg Thr Tyr Gly Ala
                595   600   605

Lys Ser Asp Ile Ile Tyr Val Gln Thr Asp Ala Thr Asn Pro Ser Val
    610   615   620

Pro Leu Asp Pro Ile Ser Val Ser Asn Ser Ser Ser Gln Ile Ile Leu
625   630   635   640

Lys Trp Lys Pro Pro Ser Asp Pro Asn Gly Asn Ile Thr His Tyr Leu
                645   650   655

Val Phe Trp Glu Arg Gln Ala Glu Asp Ser Glu Leu Phe Glu Leu Asp
                660   665   670

Tyr Cys Leu Lys Gly Leu Lys Leu Pro Ser Arg Thr Trp Ser Pro Pro
  .   675   680   685

Phe Glu Ser Glu Asp Ser Gln Lys His Asn Gln Ser Glu Tyr Glu Asp
    690   695   700

Ser Ala Gly Glu Cys Cys Ser Cys Pro Lys Thr Asp Ser Gln Ile Leu
705   710   715   720

Lys Glu Leu Glu Glu Ser Ser Phe Arg Lys Thr Phe Glu Asp Tyr Leu
            725   730   735

His Asn Val Val Phe Val Pro Arg Lys Thr Ser Ser Gly Thr Gly Ala
            740   745   750

Glu Asp Pro Arg Pro Ser Arg Lys Arg Ser Leu Gly Asp Val Gly
            755   760   765

Asn Val Thr Val Ala Val Pro Thr Val Ala Ala Phe Pro Asn Thr Ser
770   775   780

Ser Thr Ser Val Pro Thr Ser Pro Glu Glu His Arg Pro Phe Glu Lys
785   790   795   800

Val Val Asn Lys Glu Ser Leu Val Ile Ser Gly Leu Arg His Phe Thr
            805   810   815

Gly Tyr Arg Ile Glu Leu Gln Ala Cys Asn Gln Asp Thr Pro Glu Glu
            820   825   830

Arg Cys Ser Val Ala Ala Tyr Val Ser Ala Arg Thr Met Pro Glu Ala
            835   840   845

Lys Ala Asp Asp Ile Val Gly Pro Val Thr His Glu Ile Phe Glu Asn
850   855   860

Asn Val Val His Leu Met Trp Gln Glu Pro Lys Glu Pro Asn Gly Leu
865   870   875   880

Ile Val Leu Tyr Glu Val Ser Tyr Arg Arg Tyr Gly Asp Glu Glu Leu
            885   890   895

His Leu Cys Val Ser Arg Lys His Phe Ala Leu Glu Arg Gly Cys Arg
            900   905   910

Leu Arg Gly Leu Ser Pro Gly Asn Tyr Ser Val Arg Ile Arg Ala Thr
            915   920   925

Ser Leu Ala Gly Asn Gly Ser Trp Thr Glu Pro Thr Tyr Phe Tyr Val
            930   935   940

Thr Asp Tyr Leu Asp Val Pro Ser Asn Ile Ala Lys Val Asp Gly Cys
945   950   955   960

166

```
Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe
            965                 970                 975


Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val
        980                 985                 990


Thr Cys Val Val Val Asp Ile Ser  Lys Asp Asp Pro Glu  Val Gln Phe
        995                 1000                1005


Ser Trp  Phe Val Asp Asp Val  Glu Val His Thr Ala  Gln Thr Gln
    1010             1015                1020


Pro Arg  Glu Glu Gln Phe Asn  Ser Thr Phe Arg Ser  Val Ser Glu
    1025             1030                1035


Leu Pro  Ile Met His Gln Asp  Trp Leu Asn Gly Lys  Glu Phe Lys
    1040             1045                1050


Cys Arg  Val Asn Ser Ala Ala  Phe Pro Ala Pro Ile  Glu Lys Thr
    1055             1060                1065


Ile Ser  Lys Thr Lys Gly Arg  Pro Lys Ala Pro Gln  Val Tyr Thr
    1070             1075                1080


Ile Pro  Pro Pro Lys Glu Gln  Met Ala Lys Asp Lys  Val Ser Leu
    1085             1090                1095


Thr Cys  Met Ile Thr Asp Phe  Phe Pro Glu Asp Ile  Thr Val Glu
    1100             1105                1110


Trp Gln  Trp Asn Gly Gln Pro  Ala Glu Asn Tyr Lys  Asn Thr Gln
    1115             1120                1125


Pro Ile Met Asp Thr Asp Gly  Ser Tyr Phe Val Tyr  Ser Lys Leu
    1130             1135                1140


Asn Val  Gln Lys Ser Asn Trp  Glu Ala Gly Asn Thr  Phe Thr Cys
    1145             1150                1155


Ser Val  Leu His Glu Gly Leu  His Asn His His Thr  Glu Lys Ser
    1160             1165                1170


Leu Ser  His Ser Pro Gly Lys
    1175             1180


<210>  233
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```
<211>  1062
<212>  PRT
<213>  Artificial

<220>
<223>  hu IGF-1R:avidin

<400>  233
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Met Lys Ser Gly Ser Gly Gly Gly Ser Pro Thr Ser Leu Trp Gly Leu
1   5   10   15

Leu Phe Leu Ser Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile
            20   25   30

Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg
            35   40   45

Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile
        50   55   60

Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val
65   70   75   80

Ile Thr Glu Tyr Leu Leu Leu Phe Arg Val Ala Gly Leu Glu Ser Leu
                85   90   95

Gly Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Trp Lys Leu Phe
            100   105   110

Tyr Asn Tyr Ala Leu Val Ile Phe Glu Met Thr Asn Leu Lys Asp Ile
            115   120   125

Gly Leu Tyr Asn Leu Arg Asn Ile Thr Arg Gly Ala Ile Arg Ile Glu
        130   135   140

Lys Asn Ala Asp Leu Cys Tyr Leu Ser Thr Val Asp Trp Ser Leu Ile
145   150   155   160

Leu Asp Ala Val Ser Asn Asn Tyr Ile Val Gly Asn Lys Pro Pro Lys
                165   170   175

Glu Cys Gly Asp Leu Cys Pro Gly Thr Met Glu Glu Lys Pro Met Cys
            180   185   190

Glu Lys Thr Thr Ile Asn Asn Glu Tyr Asn Tyr Arg Cys Trp Thr Thr
            195   200   205

```
Asn Arg Cys Gln Lys Met Cys Pro Ser Thr Cys Gly Lys Arg Ala Cys
    210                 215             220

Thr Glu Asn Asn Glu Cys Cys His Pro Glu Cys Leu Gly Ser Cys Ser
225                 230             235                 240

Ala Pro Asp Asn Asp Thr Ala Cys Val Ala Cys Arg His Tyr Tyr Tyr
            245             250             255

Ala Gly Val Cys Val Pro Ala Cys Pro Pro Asn Thr Tyr Arg Phe Glu
            260             265             270

Gly Trp Arg Cys Val Asp Arg Asp Phe Cys Ala Asn Ile Leu Ser Ala
        275             280             285

Glu Ser Ser Asp Ser Glu Gly Phe Val Ile His Asp Gly Glu Cys Met
    290             295             300

Gln Glu Cys Pro Ser Gly Phe Ile Arg Asn Gly Ser Gln Ser Met Tyr
305             310             315             320

Cys Ile Pro Cys Glu Gly Pro Cys Pro Lys Val Cys Glu Glu Glu Lys
            325             330             335

Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly
        340             345             350

Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn
    355             360             365

Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val
    370             375             380

Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser
385             390             395             400

Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly
            405             410             415

Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp
            420             425             430

Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe
    435             440             445

Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu
```

```
        450                    455                    460


Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg
465               470               475                   480


Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr
                485               490                   495


Ser Thr Thr Thr Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr
            500               505               510


Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys
        515               520               525


Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys
    530               535               540


Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys
545               550               555                   560


Asp Val Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln
                565               570               575


Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp
            580               585               590


His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala
        595               600               605


Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser
    610               615               620


Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn
625               630               635                   640


Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr
                645               650               655


Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys
            660               665               670


Tyr Ala Asp Gly Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys
        675               680               685


Thr Glu Val Cys Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys
    690               695               700
```

170

Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr Arg Lys
705   710   715   720

Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu
                725   730   735

Arg Lys Arg Arg Asp Val Met Gln Val Ala Asn Thr Thr Met Ser Ser
            740   745   750

Arg Ser Arg Asn Thr Thr Ala Ala Asp Thr Tyr Asn Ile Thr Asp Pro
        755   760   765

Glu Glu Leu Glu Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp Asn
    770   775   780

Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr Arg
785   790   795   800

Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser
            805   810   815

Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala Asp
        820   825   830

Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser Ile
        835   840   845

Phe Leu Lys Trp Pro Glu Pro Glu Asn Pro Asn Gly Leu Ile Leu Met
    850   855   860

Tyr Glu Ile Lys Tyr Gly Ser Gln Val Glu Asp Gln Arg Glu Cys Val
865   870   875   880

Ser Arg Gln Glu Tyr Arg Lys Tyr Gly Gly Ala Lys Leu Asn Arg Leu
            885   890   895

Asn Pro Gly Asn Tyr Thr Ala Arg Ile Gln Ala Thr Ser Leu Ser Gly
            900   905   910

Asn Gly Ser Trp Thr Asp Pro Val Phe Phe Tyr Val Gln Ala Lys Thr
        915   920   925

Gly Tyr Glu Ala Ala Ala Ala Arg Lys Cys Ser Leu Thr Gly Lys Trp
    930   935   940

```
Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn Ser Lys
945             950             955                     960


Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr Ser Asn
                965             970             975


Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile Asn Lys
            980             985             990


Arg Thr Gln Pro Thr Phe Gly Phe  Thr Val Asn Trp Lys  Phe Ser Glu
        995             1000            1005


Ser Thr  Thr Val Phe Thr Gly  Gln Cys Phe Ile Asp  Arg Asn Gly
    1010            1015            1020


Lys Glu  Val Leu Lys Thr Met  Trp Leu Leu Arg Ser  Ser Val Asn
    1025            1030            1035


Asp Ile  Gly Asp Asp Trp Lys  Ala Thr Arg Val Gly  Ile Asn Ile
    1040            1045            1050


Phe Thr  Arg Leu Arg Thr Gln  Lys Glu
    1055            1060


<210>   234
<211>   107
<212>   PRT
<213>   Artificial;

<400>   234

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5               10                      15


Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20              25              30


Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35              40              45


Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50              55              60


Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65              70              75                      80


Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
```

                    85   90   95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100   105

<210> 235
<211> 330
<212> PRT
<213> Artificial

<220>
<223> heavy chain constant region

<400> 235

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1   5   10   15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20   25   30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35   40   45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50   55   60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65   70   75   80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85   90   95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100   105   110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115   120   125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130   135   140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145   150   155   160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165   170   175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180   185   190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
            195   200   205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210   215   220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225   230   235   240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
            245   250   255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260   265   270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
            275   280   285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290   295   300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305   310   315   320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            325   330

<210> 236
<211> 16
<212> PRT
<213> Artificial

<220>
<223> light chain CDR1

<220>
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<223> x is serine or threonine residue

<220>
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<222> (10)..(10)
<223> x is asparagine, serine or histidine residue

<220>
<221> MISC_FEATURE

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<222>  (14)..(14)
<223>  x is tyrosine or phenylalanine residue

<220>
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<222>  (16)..(16)
<223>  x is aspartate or asparagine residue

<400>  236

Arg Ser Ser Gln Ser Leu Leu His Xaa Xaa Gly Tyr Asn Xaa Leu Xaa
1               5                   10                  15


<210>  237
<211>  13
<212>  PRT
<213>  Artificial

<220>
<223>  light chain CDR1


<220>
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<223>  x is serine or aspartate residue

<220>
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<222>  (8)..(8)
<223>  x is alanine or aspartate residue

<220>
<221>  MISC_FEATURE
<222>  (9)..(9)
<223>  x is serine or asparagine residue

<400>  237

Thr Arg Ser Ser Gly Xaa Ile Xaa Xaa Asn Tyr Val Gln
1               5                   10


<210>  238
<211>  11
<212>  PRT
<213>  Artificial

<220>
<223>  light chain CDR1


<220>
<221>  MISC_FEATURE
<222>  (5)..(5)
<223>  x is glycine or serine residue

<220>
<221>  MISC_FEATURE
<222>  (6)..(6)
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<223>   x is isoleucine, valine or proline residue

<220>
<221>   MISC_FEATURE
<222>   (7)..(7)
<223>   x is  serine, glycine or tyrosine residue

<220>
<221>   MISC_FEATURE
<222>   (8)..(8)
<223>   x is any amino acid

<220>
<221>   MISC_FEATURE
<222>   (9)..(9)
<223>   x is phenylalanine, tyrosine, asparagine or tryptophan residue

<220>
<221>   MISC_FEATURE
<222>   (11)..(11)
<223>   x is  alanine or asparagine residue

<400>   238

Arg Ala Ser Gln Xaa Xaa Xaa Xaa Xaa Leu Xaa
1               5                   10


<210>   239
<211>   7
<212>   PRT
<213>   Artificial

<220>
<223>   light chain CDR2


<220>
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<222>   (2)..(2)
<223>   x is glycine or valine residue

<220>
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<223>   x is serine or phenylalanine residue

<220>
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<222>   (4)..(4)
<223>   x is asparagine, tyrosine or threonine residue

<220>
<221>   MISC_FEATURE
<222>   (6)..(6)
<223>   x is alanine or aspartate residue

<400>   239

Leu Xaa Xaa Xaa Arg Xaa Ser
1               5
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```
<210>  240
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<212>  PRT
<213>  Artificial

<220>
<223>  light chain CDR2


<220>
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<223>  x is alanine or threonine residue

<220>
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<222>  (4)..(4)
<223>  x is threonine or glycine residue

<220>
<221>  MISC_FEATURE
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<223>  x is glutamine or glutamate residue

<400>  240

Ala Xaa Ser Xaa Leu Xaa Ser
1               5


<210>  241
<211>  7
<212>  PRT
<213>  Artificial

<220>
<223>  light chain CDR2


<220>
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<223>  x is glutamate, glutamine or glycine residue

<220>
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<222>  (2)..(2)
<223>  x is aspartate or lysine residue

<220>
<221>  MISC_FEATURE
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<223>  x is any amino acid residue

<400>  241

Xaa Xaa Asn Xaa Arg Pro Ser
1               5
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<210>  242
<211>  9
<212>  PRT
<213>  Artificial

<220>
<223>  light chain CDR3


<220>
<221>  MISC_FEATURE
<222>  (2)..(2)
<223>  x is glutamine or glutamate residue

<220>
<221>  MISC_FEATURE
<222>  (3)..(3)
<223>  x is alanine, glycine, serine or threonine residue

<220>
<221>  MISC_FEATURE
<222>  (4)..(4)
<223>  x is  leucine or threonine residue

<220>
<221>  MISC_FEATURE
<222>  (5)..(5)
<223>  x is glutamine, glutamate or histidine residue

<220>
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<223>  x is threonine, tryptophan, methionine or valine residue

<220>
<221>  MISC_FEATURE
<222>  (8)..(8)
<223>  x is  nonpolar side chain

<220>
<221>  MISC_FEATURE
<222>  (9)..(9)
<223>  x is threonine, serine or alanine residue

<400>  242

Met Xaa Xaa Xaa Xaa Xaa Pro Xaa Xaa
1                   5


<210>  243
<211>  9
<212>  PRT
<213>  Artificial

<220>
<223>  light chain CDR3


<220>
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<223>   x is arginine, serine, leucine or alanine residue

<220>
<221>   MISC_FEATURE
<222>   (4)..(4)
<223>   x is asparagine, serine or histidine residue

<220>
<221>   MISC_FEATURE
<222>   (5)..(5)
<223>   x is serine or asparagine residue

<220>
<221>   MISC_FEATURE
<222>   (6)..(6)
<223>   x is nonpolar side chain

<220>
<221>   MISC_FEATURE
<222>   (8)..(8)
<223>   x is leucine, isoleucine, tyrosine or tryptophan residue

<400>   243

Gln Gln Xaa Xaa Xaa Xaa Pro Xaa Thr
1                   5


<210>   244
<211>   10
<212>   PRT
<213>   Artificial

<220>
<223>   light chain CDR3


<220>
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<223>   x is aspartate or glutamine residue

<220>
<221>   MISC_FEATURE
<222>   (6)..(6)
<223>   x is serine or aspartate residue

<220>
<221>   MISC_FEATURE
<222>   (8)..(8)
<223>   x is glutamine, valine or tryptophan residue

<220>
<221>   MISC_FEATURE
<222>   (9)..(9)
<223>   x is arginine  residue or no residue

<400>   244
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Gln Ser Tyr Xaa Ser Xaa Asn Xaa Xaa Val
1   5   10

<210> 245
<211> 6
<212> PRT
<213> Artificial

<220>
<223> heavy chain CDR1

<220>
<221> MISC_FEATURE
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<223> serine residue or no residue

<220>
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<222> (2)..(2)
<223> x is serine or asparagine residue

<220>
<221> MISC_FEATURE
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<223> x is asparagine and isoleucine residue

<400> 245

Xaa Xaa Xaa Trp Trp Ser
1   5

<210> 246
<211> 5
<212> PRT
<213> Artificial

<220>
<223> heavy chain CDR1

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<223> x is glycine, asparagine or aspartate residue

<220>
<221> MISC_FEATURE
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<223> x is tyrosine or phenylalanine residue

<400> 246

Xaa Xaa Tyr Trp Ser
1   5

<210> 247
<211> 5

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<212>  PRT
<213>  Artificial

<220>
<223>  heavy chain CDR1


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<220>
<221>  MISC_FEATURE
<222>  (4)..(4)
<223>  x is methionine or isoleucine residue

<220>
<221>  MISC_FEATURE
<222>  (5)..(5)
<223>  x is serine or histidine residue

<400>  247

Ser Tyr Xaa Xaa Xaa
1                5


<210>  248
<211>  16
<212>  PRT
<213>  Artificial

<220>
<223>  heavy chain CDR2


<220>
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<220>
<221>  MISC_FEATURE
<222>  (2)..(2)
<223>  x is isoleucine or valine residue

<220>
<221>  MISC_FEATURE
<222>  (3)..(3)
<223>  x is tyrosine, asparagine or serine residue

<220>
<221>  MISC_FEATURE
<222>  (4)..(4)
<223>  x is histidine, tryosine, aspartate,or proline residue

<220>
<221>  MISC_FEATURE
<222>  (5)..(5)
<223>  x is  serine or arginine residue
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<220>
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<223> x is serine or arginine residue

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> x is asparagine or tyrosine residue

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> x is lysine or glutamate residue

<400> 248

Xaa Xaa Xaa Xaa Xaa Gly Xaa Thr Xaa Tyr Asn Pro Ser Leu Xaa Ser
1   5   10   15

<210> 249
<211> 17
<212> PRT
<213> Artificial

<220>
<223> heavy chain CDR2

<220>
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<223> x is threonine, alanine, valine or tyrosine residue

<220>
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<222> (4)..(4)
<223> x is glycine, serine or tyrosine residue

<220>
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<223> x is serine, asparagine or aspartate residue

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> x is glycine or serine residue

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> x is glycine, serine or aspartate residue

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> x is serine, threonine or asparagine residue

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<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> x is threonine, lysine or isoleucine residue

<400> 249

Xaa Ile Ser Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Ala Asp Ser Val Lys
1               5                   10                  15


Gly



<210> 250
<211> 12
<212> PRT
<213> Artificial

<220>
<223> heavy chain CDR3


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<223> x is glutamate or no residue

<220>
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<222> (2)..(2)
<223> x is tyrosine, glycine or serine or no residue

<220>
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<223> x is serine, asparagine, tryptophan or glutamate or no residue

<220>
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<223> x is serine, aspartate, tryptophan, alanine, arginine, threonine,
      glutamine, leucine or glutamate or no residue

<220>
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<222> (5)..(5)
<223> x is serine, glycine, asparagine, threonine, tryptophan, alanine,
      valine or isoleucine residue

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> x is arginine, glutamine, tyosine, valine, alanine, glycine,
      serine, phenylalanine or tryptophan residue

<220>
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<222> (7)..(7)
<223> x is leucine, asparagine, aspartate, threonine, tryptophan,
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tyrosine, valine, alanine, or histidine residue

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<222>  (8)..(9)
<223>  x is aspartate, serine, asparagine or glutamine residue

<220>
<221>  MISC_FEATURE
<222>  (9)..(9)
<223>  x is alanine or proline residue

<400>  250

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Phe Asp Ile
1                   5                   10


<210>  251
<211>  14
<212>  PRT
<213>  Artificial

<220>
<223>  heavy chain CDR3


<220>
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<222>  (1)..(1)
<223>  x is alanine or no residue

<220>
<221>  MISC_FEATURE
<222>  (2)..(2)
<223>  x is glutamate, tryosine or glycine or no residue

<220>
<221>  MISC_FEATURE
<222>  (3)..(3)
<223>  x is serine, asparagine, tryptophan, glutamate or no residue

<220>
<221>  MISC_FEATURE
<222>  (4)..(4)
<223>  x is aspartate, glycine, serine, or valine residue, or no residue

<220>
<221>  MISC_FEATURE
<222>  (5)..(5)
<223>  x is serine, glycine, or aspartate residue, or no residue

<220>
<221>  MISC_FEATURE
<222>  (6)..(6)
<223>  x is glycine, phenylalanine, aspartate, serine, tryptophan, or
       tyrosine residue, or no residue

<220>
<221>  MISC_FEATURE
<222>  (7)..(7)
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<223>  x i is a tyrosine, tryptophan, serine, or aspartate residue, or
       no residue


<220>
<221>  MISC_FEATURE
<222>  (8)..(8)
<223>  x is aspartate, arginine, serine, glycine, tyrosine, or
       tryptophan residue


<220>
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<222>  (9)..(9)
<223>  x is tyrosine, isoleucine, leucine, phenylalanine, or lysine
       residue


<220>
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<222>  (10)..(10)
<223>  x is tyrosine, phenylalanine, aspartate, or glycine residue


<220>
<221>  MISC_FEATURE
<222>  (11)..(11)
<223>  x is glycine, tyrosine, or asparagine residue


<400>  251

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Met Asp Val
1                   5                   10


<210>  252
<211>  11
<212>  PRT
<213>  Artificial


<220>
<223>  heavy chain CDR3


<220>
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<223>  x is aspartate or valine residue, or no residue


<220>
<221>  MISC_FEATURE
<222>  (2)..(2)
<223>  x is glycine, tyrosine, arginine, or aspartate residue, or no
       residue,


<220>
<221>  MISC_FEATURE
<222>  (3)..(3)
<223>  x is asparagine, leucine, glycine, isoleucine, serine, valine,
       phenylalanine, or tyrosine residue, or no residue


<220>
<221>  MISC_FEATURE
<222>  (4)..(4)
<223>  x is leucine, serine, tryptophan, alanine, tyrosine, isoleucine,
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glycine, or aspartate residue, or no residue

<220>
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<222> (5)..(5)
<223> x is glycine, alanine, tyrosine, serine, aspartate, or leucine
residue

<220>
<221> MISC_FEATURE
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<223> x is valine, alanine, glycine, threonine, proline, histidine, or
glutamine residue

<220>
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<223> x is glutamate, glycine, serine, aspartate, glycine, valine,
tryptophan, histidine, or arginine residue

<220>
<221> MISC_FEATURE
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<223> x is glutamine, alanine, glycine, tyrosine, proline, leucine,
aspartate, or serine residue

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> x is nonpolar side chain residue

<220>
<221> MISC_FEATURE
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<223> x is aspartate or alanine residue

<400> 252

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr
1   5   10

<210> 253
<211> 14
<212> PRT
<213> Artificial

<220>
<223> Heavy chain CDR3

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<223> x is glycine residue, or no residue

<220>
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<223> x is proline residue, or no residue

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<220>
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<223>  x is arginine or aspartate residue, or no residue

<220>
<221>  MISC_FEATURE
<222>  (4)..(4)
<223>  x is histidine or proline residue

<220>
<221>  MISC_FEATURE
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<223>  x is arginine or glycine residue

<220>
<221>  MISC_FEATURE
<222>  (6)..(6)
<223>  x is arginine, serine, or phenylalanine residue

<220>
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<222>  (7)..(7)
<223>  x is aspartate or serine residue

<220>
<221>  MISC_FEATURE
<222>  (8)..(8)
<223>  x is glycine, tryptophan, or tyrosine residue

<220>
<221>  MISC_FEATURE
<222>  (9)..(9)
<223>  x is tyrosine or alanine residue

<220>
<221>  MISC_FEATURE
<222>  (10)..(10)
<223>  x is asparagine or tryptophan residue

<220>
<221>  MISC_FEATURE
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<223>  x is asparagine or leucine residue

<400>  253

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Phe Asp Xaa
1               5                   10


<210>  254
<211>  15
<212>  PRT
<213>  Artificial

<220>
<223>  heavy chain CDR3


<220>
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<220>
<221>  MISC_FEATURE
<222>  (2)..(2)
<223>  x is asparagine or glycine residue, or no residue

<220>
<221>  MISC_FEATURE
<222>  (3)..(3)
<223>  x is tyrosine or a leucine residue, or no residue

<220>
<221>  MISC_FEATURE
<222>  (4)..(4)
<223>  x is a tyrosine or glycine residue, or no residue

<220>
<221>  MISC_FEATURE
<222>  (8)..(8)
<223>  x is a glycine, serine, or valine residue

<220>
<221>  MISC_FEATURE
<222>  (9)..(9)
<223>  x is tyrosine, phenylalanine, tryptophan, or glutamine residue,
       or no residue

<220>
<221>  MISC_FEATURE
<222>  (10)..(10)
<223>  x is tyrosine, glycine, or isoleucine residue, or no residue

<220>
<221>  MISC_FEATURE
<222>  (11)..(11)
<223>  x is tyrosine, leucine, or glycine residue, or no residue

<220>
<221>  MISC_FEATURE
<222>  (12)..(12)
<223>  x is methionine,  glycine, or phenylalanine residue, or no
       residue

<220>
<221>  MISC_FEATURE
<222>  (13)..(13)
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<220>
<221>  MISC_FEATURE
<222>  (14)..(14)
<223>  x is  a valine,aspartate,  or tyrosine residue, or no residue

<220>
<221>  MISC_FEATURE
<222>  (15)..(15)
<223>  x is  a valine residue, or no residue
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<400> 254

Xaa Xaa Xaa Xaa Asp Ser Ser Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1   5   10   15

<210> 255
<211> 8
<212> DNA
<213> Artificial

<220>
<223> polypeptide

<400> 255
dykddddk   8

<210> 256
<211> 37
<212> DNA
<213> Artificial

<220>
<223> nucleic acid

<400> 256
agcaagcttc caccatgaag tctggctccg gaggagg   37

<210> 257
<211> 36
<212> DNA
<213> Artificial

<220>
<223> nucleic acid

<400> 257
atttgtcgac ttcgtccaga tggatgaagt tttcat   36

<210> 258
<211> 3486
<212> DNA
<213> Artificial

<220>
<223> nucleic acid

<400> 258
atgaagtctg gctccggagg agggtccccg acctcgctgt ggggggctcct gtttctctcc   60

gccgcgctct cgctctggcc gacgagtgga gaaatctgcg ggccaggcat cgacatccgc 120

aacgactatc agcagctgaa gcgcctggag aactgcacgg tgatcgaggg ctacctccac 180

atcctgctca tctccaaggc cgaggactac cgcagctacc gcttccccaa gctcacggtc 240

attaccgagt acttgctgct gttccgagtg ctggcctcg agagcctcgg agacctcttc 300

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cccaacctca cggtcatccg cggctggaaa ctcttctaca actacgccct ggtcatcttc    360

gagatgacca atctcaagga tattgggctt tacaacctga ggaacattac tcgggggggcc    420

atcaggattg agaaaaatgc tgacctctgt tacctctcca ctgtggactg gtccctgatc    480

ctggatgcgg tgtccaataa ctacattgtg gggaataagc ccccaaagga atgtggggac    540

ctgtgtccag ggaccatgga ggagaagccg atgtgtgaga agaccaccat caacaatgag    600

tacaactacc gctgctggac cacaaaccgc tgccagaaaa tgtgcccaag cacgtgtggg    660

aagcgggcgt gcaccgagaa caatgagtgc tgccaccccg agtgcctggg cagctgcagc    720

gcgcctgaca cgacacggc ctgtgtagct tgccgccact actactatgc cggtgtctgt    780

gtgcctgcct gcccgcccaa cacctacagg tttgagggct ggcgctgtgt ggaccgtgac    840

ttctgcgcca acatcctcag cgccgagagc agcgactccg aggggtttgt gatccacgac    900

ggcgagtgca tgcaggagtg cccctcgggc ttcatccgca acggcagcca gagcatgtac    960

tgcatccctt gtgaaggtcc ttgcccgaag gtctgtgagg aagaaaagaa aacaaagacc   1020

attgattctg ttacttctgc tcagatgctc caaggatgca ccatcttcaa gggcaatttg   1080

ctcattaaca tccgacgggg gaataacatt gcttcagagc tggagaactt catggggctc   1140

atcgaggtgg tgacgggcta cgtgaagatc cgccattctc atgccttggt ctccttgtcc   1200

ttcctaaaaa accttcgcct catcctagga gaggagcagc tagaagggaa ttactccttc   1260

tacgtcctcg acaaccagaa cttgcagcaa ctgtgggact gggaccaccg caacctgacc   1320

atcaaagcag ggaaaatgta ctttgctttc aatcccaaat tatgtgtttc cgaaatttac   1380

cgcatggagg aagtgacggg gactaaaggg cgccaaagca aggggacat aaacaccagg   1440

aacaacgggg agagagcctc ctgtgaaagt gacgtcctgc atttcacctc caccaccacg   1500

tcgaagaatc gcatcatcat aacctggcac cggtaccggc cccctgacta cagggatctc   1560

atcagcttca ccgtttacta caaggaagca ccctttaaga atgtcacaga gtatgatggg   1620

caggatgcct gcggctccaa cagctggaac atggtggacg tggacctccc gcccaacaag   1680

gacgtggagc ccggcatctt actacatggg ctgaagccct ggactcagta cgccgtttac   1740

gtcaaggctg tgaccctcac catggtggag aacgaccata tccgtggggc caagagtgag   1800

atcttgtaca ttcgcaccaa tgcttcagtt ccttccattc ccttggacgt tctttcagca   1860

tcgaactcct cttctcagtt aatcgtgaag tggaaccctc cctctctgcc caacggcaac   1920

ctgagttact acattgtgcg ctggcagcgg cagcctcagg acggctacct ttaccggcac   1980

aattactgct ccaaagacaa aatccccatc aggaagtatg ccgacggcac catcgacatt   2040

gaggaggtca cagagaaccc caagactgag gtgtgtggtg gggagaaagg gccttgctgc   2100

gcctgcccca aaactgaagc cgagaagcag gccgagaagg aggaggctga ataccgcaaa   2160
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190

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gtctttgaga atttcctgca caactccatc ttcgtgccca gacctgaaag gaagcggaga   2220

gatgtcatgc aagtggccaa caccaccatg tccagccgaa gcaggaacac cacggccgca   2280

gacacctaca acatcactga cccggaagag ctggagacag agtacccttt ctttgagagc   2340

agagtggata acaaggagag aactgtcatt tctaaccttc ggcctttcac attgtaccgc   2400

atcgatatcc acagctgcaa ccacgaggct gagaagctgg gctgcagcgc ctccaacttc   2460

gtctttgcaa ggactatgcc cgcagaagga gcagatgaca ttcctgggcc agtgacctgg   2520

gagccaaggc ctgaaaactc catcttttta aagtggccgg aacctgagaa tcccaatgga   2580

ttgattctaa tgtatgaaat aaaatacgga tcacaagttg aggatcagcg agaatgtgtg   2640

tccagacagg aatacaggaa gtatggaggg gccaagctaa accggctaaa cccgggggaac  2700

tacacagccc ggattcaggc cacatctctc tctgggaatg ggtcgtggac agatcctgtg   2760

ttcttctatg tccaggccaa aacaggatat gaaaacttca tccatctgga cgaagtcgac   2820

ggttgtaagc cttgcatatg tacagtccca gaagtatcat ctgtcttcat cttcccccca   2880

aagcccaagg atgtgctcac cattactctg actcctaagg tcacgtgtgt tgtggtagac   2940

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acagctcaga cgcaaccccg ggaggagcag ttcaacagca ctttccgctc agtcagtgaa   3060

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ccacaggtgt acaccattcc acctcccaag gagcagatgg ccaaggataa agtcagtctg   3240

acctgcatga taacagactt cttccctgaa gacattactg tggagtggca gtggaatggg   3300

cagccagcgg agaactacaa gaacactcag cccatcatgg acacagatgg ctcttacttc   3360

gtctacagca agctcaatgt gcagaagagc aactgggagg caggaaatac tttcacctgc   3420

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ggtaaa                                                             3486
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cggaacaacc tcactaggtt gcatgagctg gagaattgct ctgtcatcga aggacacttg     180

cagatactct tgatgttcaa aacgaggccc gaagatttcc gagacctcag tttccccaaa     240

ctcatcatga tcactgatta cttgctgctc ttccgggtct atgggctcga gagcctgaag     300

gacctgttcc ccaacctcac ggtcatccgg ggatcacgac tgttctttaa ctacgcgctg     360

gtcatcttcg agatggttca cctcaaggaa ctcggcctct acaacctgat gaacatcacc     420

cggggttctg tccgcatcga gaagaacaat gagctctgtt acttggccac tatcgactgg     480

tcccgtatcc tggattccgt ggaggataat cacatcgtgt tgaacaaaga tgacaacgag     540

gagtgtggag acatctgtcc gggtaccgcg aagggcaaga ccaactgccc cgccaccgtc     600

atcaacgggc agtttgtcga acgatgttgg actcatagtc actgccagaa agtttgcccg     660

accatctgta agtcacacgg ctgcaccgcc gaaggcctct gttgccacag cgagtgcctg     720

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gacggcaggt gtgtggagac ctgcccgccc ccgtactacc acttccagga ctggcgctgt     840

gtgaacttca gcttctgcca ggacctgcac cacaaatgca gaactcgcg gaggcagggc     900

tgccaccagt acgtcattca caacaacaag tgcatccctg agtgtccctc cgggtacacg     960

atgaattcca gcaacttgct gtgcaccca tgcctgggtc cctgtcccaa ggtgtgccac     1020

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accgtcatca cgggagtct gatcatcaac attcgaggag gcaacaatct ggcagctgag     1140

ctagaagcca acctcggcct cattgaagaa atttcagggt atctaaaaat ccgccgatcc     1200

tacgctctgg tgtcactttc cttcttccgg aagttacgtc tgattcgagg agagaccttg     1260
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gaaattggga actactcctt ctatgccttg gacaaccaga acctaaggca gctctgggac    1320

tggagcaaac acaacctcac caccactcag gggaaactct tcttccacta taaccccaaa    1380

ctctgcttgt cagaaatcca caagatggaa gaagtttcag gaaccaaggg gcgccaggag    1440

agaaacgaca ttgccctgaa gaccaatggg gacaaggcat cctgtgaaaa tgagttactt    1500

aaattttctt acattcggac atcttttgac aagatcttgc tgagatggga gccgtactgg    1560

cccccccgact tccgagacct cttggggttc atgctgttct acaaagaggc cccttatcag    1620

aatgtgacgg agttcgatgg gcaggatgcg tgtggttcca acagttggac ggtggtagac    1680

attgacccac ccctgaggtc caacgacccc aaatcacaga accacccagg gtggctgatg    1740

cggggtctca agccctggac ccagtatgcc atctttgtga agaccctggt caccttttcg    1800

gatgaacgcc ggacctatgg ggccaagagt gacatcattt atgtccagac agatgccacc    1860

aacccctctg tgcccctgga tccaatctca gtgtctaact catcatccca gattattctg    1920

aagtggaaac caccctccga ccccaatggc aacatcaccc actacctggt tttctgggag    1980

aggcaggcgg aagacagtga gctgttcgag ctggattatt gcctcaaagg gctgaagctg    2040

ccctcgagga cctggtctcc accattcgag tctgaagatt ctcagaagca caaccagagt    2100

gagtatgagg attcggccgg cgaatgctgc tcctgtccaa agacagactc tcagatcctg    2160

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aagccttgca tatgtacagt cccagaagta tcatctgtct tcatcttccc cccaaagccc    2940

aaggatgtgc tcaccattac tctgactcct aaggtcacgt gtgttgtggt agacatcagc    3000

aaggatgatc ccgaggtcca gttcagctgg tttgtagatg atgtggaggt gcacacagct    3060
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ttccctgccc ccatcgagaa aaccatctcc aaaaccaaag gcagaccgaa ggctccacag   3240

gtgtacacca ttccacctcc caaggagcag atggccaagg ataaagtcag tctgacctgc   3300

atgataacag acttcttccc tgaagacatt actgtggagt ggcagtggaa tgggcagcca   3360

gcggagaact acaagaacac tcagcccatc atggacacag atggctctta cttcgtctac   3420

agcaagctca atgtgcagaa gagcaactgg gaggcaggaa atactttcac ctgctctgtg   3480

ttacatgagg gcctgcacaa ccaccatact gagaagagcc tctcccactc tcctggtaaa   3540
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tgacactctc ctgtgcagcc tcgggattca ctttcagaac ctatggcatg gcctgggtcc    180

gccaggcccc aacgaagggt ctggagtggg tctcatcaat tactgctagt ggtggtacca    240

cctactatcg agactccgtg aagggccgct tcactatttt tagggataat gcaaaaagta    300

ccctatacct gcagatggac agtccgaggt ctgaggacac ggccacttat ttctgtacat    360

caatttcgga atactggggc cacggagtca tggtcaccgt ctctagtgcc tccaccaagg    420

gcccatcggt cttccccctg gcaccctcct ccaagagcac ctctgggggc acagcggccc    480

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tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac ccagacctac atctgcaacg    660

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aaactcacac atgcccaccg tgcccagcac ctgaactcct ggggggaccg tcagtcttcc    780

tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag gtcacatgcg    840

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tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa tggcaaggag tacaagtgca   1020

aggtctccaa caaagccctc ccagccccca tcgagaaaac catctccaaa gccaaagggc   1080
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agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg gactccgacg    1260

gctccttctt cctctatagc aagctcaccg tggacaagag caggtggcag caggggaacg    1320

tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag aagagcctct    1380

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<213>    Artificial

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<223>    protein

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys
            20


<210>    264
<211>    22
<212>    PRT
<213>    Artificial

<220>
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<400>    264

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15


Leu Arg Gly Ala Arg Cys
            20


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<213>    Artificial

<220>
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<220>
<223>  nucleic acid

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agcaagcttg ccgaaggtct gtgaggaag                                 29
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attgcggccg ctttaatggc cactctggtt tc   32

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agcaagcttg ggagaaatct gcgggccag   29